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RECENT ADVANCES IN OTITIS MEDIA

REPORT OF THE FOURTH RESEARCH CONFERENCE

Editor
DAVID J. LIM, MD

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INTRODUCTION

When we were planning the First International Symposium on Otitis Media with Effusion, the Planning Committee felt that a postsymposium Research Conference was needed to digest the new progress that had been made and to discuss and establish research goals for the future. The first postsymposium Research Conference, which was held May 31-June 1, 1975, in Columbus, Ohio, was a great success in promoting research and fellowship. Having the Research Conference immediately after the major symposium was an excellent means of critically analyzing the research results and focusing on research questions for the future. This format has become an institution of this meeting as a model to help focus research questions and to mobilize researchers so that rapid progress can be made in a short time. So far we have had four highly successful postsymposium Research Conferences. Each postsymposium Research Conference has advanced the field to new heights and has helped to delineate future research goals.

The fourth symposium was broadened in its scope to encompass the entire field of "otitis media." Consequently, the fourth postsymposium Research Conference also was broadened in its depth and in the number of members who were invited to participate. This reflected the vast advances this field has made in the last 4 years, the increased number of scientists with diverse backgrounds, and the multidisciplinary approach to otitis media research. The researchers represented many divergent disciplines such as otolaryngology, pediatrics, audiology, speech pathology, microbiology, immunology, biochemistry, cell biology, molecular biology, biophysics, physiology, and epidemiology.

The purpose of this Research Conference, like that of previous ones, was to assess the research accomplishments over the last 4 years, to identify the important research questions and emerging new fields, and to develop a consensus on future research goals that will serve as a useful guide for investigators and funding agencies. Developing a consensus among investigators with varying scientific backgrounds and differing disciplines has never been easy. However, it is imperative to hold this Conference to establish a consensus or to debate the differences in a constructive manner. Because of the diversity of the investigative disciplines and the large number of investigators involved in otitis media research throughout the world, it is anticipated that there will be some differing opinions. We feel strongly that the passionate discussions often stimulate more research interest and bring a healthy vitality to the research activity. Because of the differing opinions on certain topics expressed by the members of the panels, the final report has undergone a number of revisions so that it reasonably and accurately reflects the sentiments of the Panels. Where a consensus could not be developed, we included a minority report to reflect those opinions.

In the preparation of the present Research Conference report, we have attempted to generate an in-depth report of the progress made rather than listing research topics of interest, as done by some Panels in past reports, and we have made a conscious effort to include the more pertinent references generated during the last 4 years in various fields. Therefore, it is hoped that the present Research Conference report will be more meaningful as a source reference and guide. Although the final report may not be perfect, it should be taken as a basis to help develop or extend the research direction. It is also hoped that this continued effort in redefining the research goals and evaluating the past progress will help to resolve the basic and clinical problems involving otitis media and will help to entice many more researchers into this fertile field.

Because of the difficult task of completing an acceptable and useful report during the limited time of the Conference, the organizing committee regretfully had to limit the number of participants for this conference. The selection of participants was made arbitrarily, largely on the basis of their current research activities, their expertise representing various research disciplines, and their geographic representation.

It would not have been possible to have a Research Conference of this magnitude and complexity without substantial financial support. On behalf of the Planning Committee, I would like to thank especially the National Institute of Neurological and Communicative Disorders and Stroke and the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, and the Deafness Research Foundation for partially funding this Conference. We would also like to express our heartfelt thanks to Dr Ralph Naunton, Director of the Communication Disorders Program at the NINCDS, and Dr James Hill, Deputy Director of the NIAID, for taking time from their busy schedules to participate in this Conference. We also thank Dr Walter Petryshyn, Medical Director of the Deafness Research Foundation, who gave his unfailing support for the Symposium and Research

Conference. Our deepest appreciation goes to the Center for Continuing Medical Education for making the arrangements for this conference, and we are particularly indebted to Jon Hollett, Director of the Center for Continuing Medical Education, and his staff for their assistance before and during the Conference; to my associates, Drs Thomas DeMaria and Lauren Bakaletz, for coordinating many of the logistics of this Research Conference and for editing the final report; and to my administrative assistant, Teresa Martin, for editing the manuscripts. Finally, I express our profound gratitude to the participants for their hard work, particularly those who helped to write position papers and to prepare the final reports.

DAVID J. LIM, MD

SPECIAL REMARKS

RALPH F. NAUNTON, MD

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DISORDERS AND STROKE

The National Institute of Neurological and Communicative Disorders and Stroke once again welcomes the opportunity to be involved in the Research Conference on Otitis Media.

The past history and the present momentum of this conference serve as excellent examples of productive collaboration between the NINCDS and investigators working in scientific areas related to otitis media. Individual investigators and clinicians saw, many years ago, that the very important clinical problem of otitis media was seriously in need of intensive study. At the same time, it was felt that research on the broad topic was feasible and filled with promise of success.

Now, almost two decades later, there have been four international symposia on recent advances in otitis media, including the present report.[1-3] There has been great expansion of NIH support for research on otitis media and related topics; and the Institute has provided partial support for otitis media research conferences, at which groups of clinicians and scientists of international repute identify and discuss topics related to otitis media that are in need of further study.

The published proceedings of the Research Conferences continue to serve as a priceless road map for the serious investigator and, at the same time, serve to focus research initiatives and practically guarantee improvements in our understanding and management of otitis media in years to come.

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PANEL REPORTS

1A. DEFINITION AND CLASSIFICATION

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Since the last Research Conference and the publication of the report of the Panel on Definition and Classification,[1,2] no new information has been introduced to require or encourage changes in the statement. The terminology has enjoyed wide acceptance and use. Acceptance of terms or their definitions is voluntary and depends on many factors, such as the user's native language and customs and the relevance of the terms to his or her uses. It is not the Panel's purpose to force usages, but rather to suggest terms to improve clinical and scientific communication. It is incumbent upon every author or speaker to define his or her own terms when communicating with colleagues. The terms and definitions represent compromises by the Panel to encourage communication in the field.

With increasing research and increasing ability to prevent, diagnose, and treat otitis media, there will always be a need to reassess terms. The Panel agreed to define terms on clinical grounds, excluding terms used in other disciplines such as audiology, speech pathology, pathology, immunology, and bacteriology. Terms that traditionally have been accepted in certain countries are incorporated, when reasonable, as synonyms for the preferred terms.

Otitis media is defined as inflammation of the middle ear. It is classified as follows.

1. *Myringitis.* Myringitis is an inflammation of the tympanic membrane that may occur alone or in association with external otitis or otitis media.

2. *Acute Suppurative Otitis Media (Acute Purulent Otitis Media, Acute Otitis Media).* Acute suppurative otitis media refers to a clinically identifiable infection of the middle ear with sudden onset and short duration.

3. *Secretory Otitis Media (Chronic Otitis Media With Effusion, Otitis Media With Effusion, Nonsuppurative Otitis Media, Catarrh, Serous Otitis Media, Serotympanum, Mucoid Otitis Media, Mucotympanum).* Secretory otitis media refers to the presence of middle ear effusion behind an intact tympanic membrane without acute signs or symptoms. This broad term refers to a nonsuppurative or clinically noninfectious form of otitis media.

4. *Chronic Suppurative Otitis Media (Chronic Otitis Media).* Chronic suppurative otitis media refers to a chronic discharge from the middle ear through a perforation of the tympanic membrane. Suppurative refers to active clinical infection. A perforation without discharge can be an inactive stage of the infection.

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1B. EPIDEMIOLOGY AND NATURAL HISTORY

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RECENT CONTRIBUTIONS

Important new contributions during the last 5 years include the fact that age at first episode of ear disease has been identified regularly as one of the strongest predictors of recurring disease. This observation requires further investigation and explanation. Also, many investigators have identified immunologic markers strongly predictive of risk. Extensive, additional studies are required.

Important references in this field are listed.[1-29] The authors of this report believe that these references merit mention; the list is not intended to be exhaustive.

The Panel identified the following areas that require special consideration for investigations to be carried out in the near future.

1. Middle ear disease will occur at high rates in infants and children infected with human immunodeficiency virus. This fact demands urgent investigation into incidence, cause, and therapy. Infection with human immunodeficiency virus also must be considered in some populations as a confounding variable.
2. Abuse of narcotics, alcohol, and tobacco during pregnancy may change the incidence of middle ear disease in young infants. These areas require further investigation.
3. Middle ear disease occurs in all socioeconomic strata, but few studies have included truly impoverished children. New studies should be carried out in regions with such children.
4. Malnutrition as a factor contributing to middle ear disease has been little studied. Populations requiring study exist in developing countries and in some regions within industrialized countries. Future research must use objective criteria to assess nutrition.
5. Studies of various forms of day-care for young infants is now under way in many locations. These should be expanded and refined.
6. Further work is needed to describe and explain the interaction between infant nutrition and middle ear disease.
7. Passive smoking has been both incriminated and exonerated in reports of middle ear disease. Objective measurements of passive smoking are needed in future studies.
8. Epidemiologic studies of viral infection, especially of the respiratory syncytial virus, should determine whether certain viruses are associated with an unduly high risk for recurrent or persistent middle ear disease.
9. Middle ear disease in neonates has been investigated in only a limited fashion. Further work is needed to determine which factors place a neonate at high risk. Nosocomial viral infections must be considered in such studies.
10. Immunology markers for susceptibility to middle ear disease must be investigated as part of future epidemiologic studies.
11. The first year of life appears to be critically important in the epidemiology of middle ear disease. New studies must determine which variables are associated with this increased risk.
12. Allergy requires further study for its role in middle ear disease. Until a rigorous definition and also objective measures for allergy appear, future studies will be limited severely.

METHODOLOGIC ISSUES

While there are many practical limitations and trade-offs that must be made when designing and executing epidemiologic studies of otitis media, it is essential that investigators use the most rigorous methods possible. The following issues must be considered.

1. *Design*. Prevalence surveys, population-based longitudinal surveys, intensive prospective studies on well-defined groups, and retrospective case control studies have all contributed to our understanding of otitis media. No one design can answer all questions, and each has inherent strengths and limitations. Population-based studies have the advantage of representativeness, but may suffer from incorrect diagnosis or underdiagnosis. Intensive prospective studies may achieve better ascertainment of disease, but may be limited to particular clinics or institutions, and hence the results may not be widely applicable. Retrospective clinical studies are

particularly troublesome, because extent of disease in cases often is defined poorly, and absence of past ear disease in controls is similarly uncertain. These studies also suffer from problems such as recall bias.

2. *Population Description.* Countries differ with respect to many factors that contribute to occurrence of otitis media, such as child care practices, access to medical care, etc. Ethnic and cultural characteristics of the population need to be described, so that others may determine whether reported results may be generalized to other settings or countries.

3. *Selection or Formation of Control Comparison Groups.* When control groups for otitis media are selected, their source, inclusion criteria, and exclusion criteria should be specified. If comparison groups are formed from a survey or longitudinal study, then methods used to form these groups should be described clearly.

4. *Diagnostic Methods.* If otoscopy is used, criteria for diagnosis should be stated in terms that can be replicated by others, rather than in conceptual terms. Validation of otoscopists and/or interobserver agreement should be reported whenever possible. In population-based studies, validation of a sample of the diagnoses will strengthen these results. Objective diagnosis (eg, tympanometry) should be used whenever possible. This should include the identification of instruments used and criteria with established efficacy. New instruments incorporating old techniques should not be assumed to have efficacy equal to that of older instruments. The objective methods reported by Marchant et al[5] need to be confirmed and extended for children in the first 6 months of life.

5. *Degree of Disease.* Incidence and age of onset of disease are influenced highly by timing and frequency of ear examinations. These variables need to be described in detail for interpretation of the results of future studies.

6. *Definition and Measurement of Risk Factors.* Objective measurements, such as urinary nicotine levels for smoking, need to be utilized to corroborate the results of questionnaire studies. Better definition of variables also is needed. For example, day-care is a complex variable that includes numbers and ages of children, room size, etc.

7. *Analysis of Confounding Variables.* Care must be taken to use appropriate statistical methods that explore the interaction of several predictor variables as they influence an outcome variable. Simple bivariate analyses are frequently inappropriate.

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2. EUSTACHIAN TUBE AND MIDDLE EAR PHYSIOLOGY AND PATHOPHYSIOLOGY

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OBJECTIVES

The purpose of this Panel was to identify

1. Major research areas in eustachian tube and middle ear physiology and pathophysiology.
2. Recent contributions of international scientists in understanding these areas.
3. The short-term and long-term goals of these efforts.

RECENT CONTRIBUTIONS

As in the past, studies of eustachian tube and middle ear function in human populations and animal models have been performed. The major efforts were by researchers from Scandinavia, Japan, and the United States. These studies have addressed many of the issues raised in the previous panel reports, including

1. Normal middle ear pressure and gas composition.
2. Mucociliary clearance function.
3. Middle ear microcirculation and gas exchange.
4. Cyclic variation in middle ear pressure and eustachian tube function.
5. Methods of testing.

Among others specifically, this summary will focus on recent studies of eustachian tube and middle ear physiology and pathophysiology. A number of new techniques for eustachian tube ventilatory function testing have been developed and validated. Appropriate terminology for use in describing the results of these tests has been suggested, although as yet it is not standardized. These techniques include phototubometry,[1] improved methods of sonometry,[2-6] and direct intraluminal endoscopic observation.[7,8] Emphasis has been focused on studies of the transport and clearance properties of the tube,[9-11] including ciliary activity,[12-16] surfactant,[17,18] and muscular function.[19-28] A more dynamic view of tubal function was suggested by studies in neural and hormonal control, autonomic cycling,[29-31] and response to mediators.[32-34] Studies of tubal function have been extended to include its relation to the nose, nasopharynx, lungs, middle ear, and mastoid air cell system.[35-38] Animal models using species such as rats, guinea pigs, chinchillas, domestic cats, and rhesus monkeys were developed to mirror the physiology and pathophysiology of the human system.[39-57] Function tests have been performed to assess the role of eustachian tube obstruction in the development of middle ear disease.[58-60] These tests evaluated selected patients with cleft palate, nasopharyngeal carcinoma, and nasal obstruction.[61-68] Tubal obstruction was documented in patients and animals following challenges with inflammatory mediators, allergens, and rhinoviruses.[69-77] Other studies have assessed the closing failure of the tube.[78-81]

Imaging of the eustachian tube has been performed with use of new techniques.[82-86] The relationship between eustachian tube function, surgery,[87-91] and drugs[92-94] also has been assessed. Anatomic and histologic studies of the tubal system have been done (see Anatomy section, pp 19-22).

A major focus in the studies of middle ear physiology has been to describe the variation in middle ear pressure associated with gas absorption and gas composition in normal and diseased ears.[95-107] More recent studies have evaluated the middle ear mucociliary transport system.[108-111] The effect of insults to the tympanic membrane and external ear canal in animals from middle ear effusion production was described and related to mast cell distribution within the tympanic membrane.[112,113] A neurologic effect was documented.[114,115] In addition, the function of the pars flaccida was described, and the vascular and mast cell distributions within the tympanic membrane were defined in both humans and animals.[116-118]

SHORT-TERM GOALS

While these studies have furthered our understanding of the eustachian tube and middle ear physiology and pathophysiology, there are still many areas in which valid and innovative contributions can be made. Primarily, it is the consensus of this Panel that we should

1. Continue the various studies described above with emphasis on tubal dynamics, neural control, mucociliary clearance, middle ear gas composition, and virus and mediator challenges.
2. Develop methods to evaluate the significance of our more recent anatomic observations within a physiologic context.
3. Establish an accepted and useful terminology to describe the various test parameters, which will allow for the comparison of data generated in different countries and by different techniques.
4. Assess the intertest reliability of different methods of eustachian tube testing.
5. Define the significance of eustachian tube test results as to their response sensitivity and source of origin.
6. Provide a testable model for understanding middle ear function within the context of nasal, velopalatine, nasopharyngeal, tubal, systemic, and external canal environments.

LONG-TERM GOALS

Our research efforts should include the following long-term goals

1. Establish and validate diagnostic tests of the eustachian tube–middle ear system that are prognostically useful and applicable in a clinical setting.
2. Develop a fundamental understanding of the interrelationship of the various components of the middle ear system and its extensions with respect to physiology and pathophysiology.
3. Utilize the tools and understanding to rationally and objectively design nonsurgical and surgical methods for the prevention of middle ear disease.
4. Assess these interventions in a clinical population.

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3. ANATOMY, CELL BIOLOGY, AND PATHOLOGY

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OBJECTIVES

The objectives of this Panel were 1) to identify the significant contributions that have been made in the areas of anatomy, cell biology, and pathology in recent years, and 2) to recommend future research goals.

RECENT CONTRIBUTIONS

Many significant contributions to our knowledge of the tubotympanum have been made during the past 4 years since the Third International Symposium on Recent Advances in Otitis Media with Effusion in 1983.

1. *Gross Anatomy.* Several advances were made in our knowledge of the gross anatomy of the tubotympanum. One area of study has been the description of mastoid size and pneumatization and otitis media. The degree of mastoid pneumatization was correlated with secretory otitis media.[1] Children with otitis media with effusion were noted to have decreased pneumatization of the mastoid.[2] The smaller mastoid air cells seen in otitis media–prone children were felt to be a sequela of secretory otitis media, rather than a cause of the disease.[3] The other area of active investigation has been the study of the eustachian tube. In a cadaver study, an inverse correlation of mastoid pneumatization size and bougie-assessed eustachian tube caliber was found in 110 adult temporal bone specimens. In other words, the well-developed normal mastoids were associated with a smaller eustachian tube, and small mastoids, which typify the various otitis media diseases, were associated with a large eustachian tube.[4] Anatomy of the eustachian tube was reviewed,[5] and prenatal and postnatal development of the eustachian tube was described.[6] Magnetic resonance imaging of the eustachian tube[7] and cartilage shape of the eustachian tube[8] have been described. Computer-assisted image-processing techniques have been used to reconstruct three-dimensional temporal bone structures.[9,10] With use of the pneumatic flexible fiberoptic endoscope, functional anatomy of the eustachian tube in normal and pathologic conditions was studied.[11]

2. *Light Microscopic Studies.* There have been many contributions in the area of histology and histopathology of the tubotympanum. A large number of mast cells were found in the pars flaccida of the tympanic membrane and in the specific areas of the middle ear space in both humans and rats.[12] Routine conventional temporal bone histopathology has continued to add new knowledge of the tubotympanum. A method of collection, processing, and study of the entire eustachian tube and temporal bone was reported.[13] This method will be helpful to study the entire tubotympanum as a single unit. The histopathologic study of temporal bones from fetuses and newborns showed the possible effect of persistent primitive mesenchyme on the development of otitis media with effusion.[14] Because of its importance as a portal of entry of organisms or antigens to the inner ear from the middle ear, the round window has been studied extensively. Anatomy of the human round window in the normal condition[15] and in otitis media[16] was reported. Histopathology of the round window with special reference to its permeability was described.[17,18] Histopathology of the subepithelial space in otitis media was studied.[19] Temporal bone findings in silent otitis media were correlated with clinical findings.[20] A comprehensive temporal bone study failed to show a statistical difference between the size of the lumen of various portions of the eustachian tube in patients with acute or secretory otitis media and that of patients with normal ears.[21]

Histopathology of various animal models of otitis media has been described.[22-25] A quantitative analysis of middle ear and eustachian tube histopathology during experimental influenza A infection was reported.[26] A quantitative histopathologic study of eustachian tube and middle ear in otitis media has been done. Goblet cell counts have been made, and density of subepithelial seromucous glands in eustachian tube and tympanic cavity has been measured.[27] The degree of inflammation in different areas of the tympanic cavity was quantitated in human temporal bones with otitis media.[28]

3. *Electron Microscopic Studies.* Scanning and transmission electron microscopy have been helpful in detecting ultrastructural changes in the tubotympanum due to otitis media with effusion. Human eustachian tube epithelium was studied with scanning electron microscopy in normal and pathologic conditions in different age groups. From this study it was suggested that the mucociliary dysfunction might induce the accumulation of fluid in the middle ear cavity.[29] Light microscopic and ultrastructural description of disorders of experimental influenza A infection have been reported.[30] The ultrastructure of the mucus blanket in otitis media with effusion was described.[31] The histopathology of middle ear mucosa in otitis media with effusion in humans was studied with transmission electron microscopy.[32,33] An ultrastructural study of the middle ear mucosa from patients with otitis media with effusion from two different age groups showed no significant difference.[34]

4. *Immunocytochemistry.* By use of an immunocytochemical technique, lysozyme and lactoferrin were found in the chinchilla tubotympanum.[35] Lysozyme was localized primarily in the epithelial mucous cells and mucous glands, while lactoferrin was localized in the epithelial secretory (serous) cells and serous glands. Glycoconjugates in the Japanese monkey eustachian tube have been characterized.[36] Middle ear mucosa from human chronic mucoid and serous otitis media was studied and characterized with histopathologic and immunohistologic techniques.[37] Intravenously injected kanamycin was localized in the eustachian tube and middle ear mucosa with an immunocytochemical technique. Kanamycin was seen in the epithelial and subepithelial layers of the eustachian tube, but not in the tubal gland.[38] Several new peptides have emerged as neurotransmitter candidates in nerve fibers in the middle ear mucosa.[39] So far, nerve fibers containing neuropeptide Y, vasoactive intestinal peptide, peptide histidine isoleucine, substance P, neurokinin A, calcitonin gene-related peptide, and galanin have been found. These peptides seem to work within the confines of the sympathetic, parasympathetic, and sensory nervous systems.

5. *Tracer Techniques.* A few retrograde tracers, horseradish peroxidase, and true blue have been used for the study of the origin of nerve fibers to various middle ear structures. With horseradish peroxidase, the innervation of the stapedius muscle, tensor muscles, and eustachian tube muscles has been studied.[40,41] True blue and horseradish peroxidase have been used for the study of the innervation of the tympanic membrane and the middle ear mucosa. Nerve fibers seem to originate in the superior cervical ganglion and the otic, sphenopalatine, jugular, trigeminal, and cervical dorsal root ganglia at levels C-2 to C-4.[42] With horseradish peroxidase, motor and sensory innervation of the eustachian tube muscle was studied in monkeys.[43] One unexpected finding is that the fibers innervating tubal muscles project to the respiratory center.

6. *Tissue Culture Technique.* Terminal differentiation of rat middle ear epithelium was studied with a cell culture technique. Cell morphology was evaluated by phase contrast, scanning electron microscopy, and transmission electron microscopy, and cytokeratin was demonstrated by immunoblotting, immunofluorescence, and immunoperoxidase techniques.[44]

FUTURE GOALS

1. Refine computer-aided three-dimensional reconstruction of the tubotympanum and its accessory structures.
2. Pursue systematic comparative anatomic studies of tubotympanic structures.
3. Document the anatomic characteristics of various patient populations with otitis media by use of modern imaging techniques such as MRI and fiberoptics in order to correlate the anatomy with the documented clinical conditions.
4. Continue systematic and quantitative study of human temporal bone sections with otitis media, especially in relation to eustachian tube disease, particularly in high-risk groups.
5. Develop methods of establishing the origin of cellular lineage in the tubotympanum in normal and pathologic conditions.
6. Investigate cell turnover and cell kinetics of middle ear and tubal mucosa in normal and pathologic conditions. In particular, the role the basal cells play in these processes should be studied.
7. Clarify the mechanisms (such as neural, humoral, pharmacologic) involved in blood vessel regulation (dilation, constriction, and leakage) of the tubotympanum.
8. Investigate cellular regulatory mechanisms, including the production of regulatory factors by middle ear cells and cell surface receptors for these factors (eg, inflammatory mediators, both neurohumoral and pharmacologic).
9. Study the cellular responses of the middle ear mucosa and eustachian tube in the presence of mediators of inflammation such as histamine, prostaglandins, and leukotrienes.
10. Characterize the host receptors for respiratory viruses and bacteria that are related to otitis media.
11. Investigate the regulatory mechanisms of secretion of the tubotympanum in normal as well as in pathologic conditions.
12. Characterize the secretory products of the tubotympanum in respect to the nature of the mucus blanket, periciliary fluid production, and ciliary motility, as well as in respect to bio-

logic activity (eg, bacteriostatic and surface activity).
13. Establish the regulatory mechanisms of ciliary activity of the tubotympanum.
14. Study the reactivity of the subepithelial tissue components in relation to specific pathogenic stimuli in immature and mature patients.
15. Determine the role of genetic factors such as human leukocyte antigen or major histocompatibility locus class II cell surface antigen in susceptibility to otitis media.
16. Study the cellular mechanisms involved in pathogenesis of different types (stages) of the continuum of otitis media and their sequelae.
17. Study the role of the round window membrane in possible inner ear sequelae of otitis media.
18. Study further subclinical (silent) otitis media relative to pathogenesis and the continuum of development of types of otitis media.

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4. MICROBIOLOGY, IMMUNOLOGY, BIOCHEMISTRY, AND VACCINATION

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MICROBIOLOGY

During the past 5 years, significant progress has been made in several areas of microbiology and microbial immunology of middle ear disease. Many of these areas were identified as the focus of immediate work in the 1983 Research Conference report.

ROLE OF VIRUSES

The contribution of respiratory viral infections to the pathogenesis of middle ear disease has been supported further by studies from several groups. Middle ear fluid or nasal wash specimens of up to 35% to 40% of patients with acute otitis media exhibit viral antigens or infectious respiratory viruses.[1] The mechanisms by which viral infections may predispose to bacterial infections in the middle ear also have been examined. There is now increasing evidence of a close relationship between respiratory viral infections and the development of acute otitis media (with isolation of pathogenic bacteria from middle ear effusions). Recently, investigators have extended some of these earlier studies by examining the effects of viral infections on leukocyte function and middle ear pressure, and by examining the virulence of different influenza A strains in the chinchilla model. Strain differences were apparent in the effects both on leukocyte function and on subsequent bacterial infections. Results of animal studies suggest that influenza A viruses infect epithelial cells of the nasopharynx and proximal eustachian tube, but disease is seen in the distal tube and middle ear mucosa, even in the absence of middle ear effusions. Studies in experimental models also suggest that the ciliated cells in the middle ear and eustachian tube are susceptible to viral infection. Attenuated and killed influenza virus vaccines are being tested in animal models and in clinical trials for their ability to prevent upper respiratory tract infections including acute otitis media.

Another investigative approach has focused on the morphology of cilia from the nasal epithelium during viral respiratory infections in young children. It is reported that some viral infections are associated with the appearance of transient dysmorphic forms involving the ciliary microtubules.[2] Functional correlates of these changes to the development of otitis media have not been explored to date. There appears to be a relationship between experimental infection with rhinoviruses and transient eustachian tube dysfunction. The investigations also have explored the relationship between antecedent influenza viral infection and adherence of *Hemophilus influenzae* to epithelial cells. Surprisingly, in the chinchilla model, preceding viral infection resulted in decreased bacterial adherence for nontypeable *H influenzae* in the early stages of viral infection, unlike that noted for other microorganisms in several in vitro models, in which adherence was increased. Finally, respiratory syncytial virus infection of the lower respiratory tract has been associated with mast cell degranulation, histamine release, and production of leukotrienes and prostaglandins in in vitro as well as in in vivo settings. These observations suggest that viruses may function as true "allergens." Immune responses to viruses other than respiratory syncytial virus also may occur in the eustachian tube or middle ear, thus contributing to the pathogenesis of otitis media.

ROLE OF BACTERIA

Pneumococcus and *H influenzae* are still the most common bacteria cultured from acute effusions. *Moraxella (Branhamella) catarrhalis* is cultured occasionally, but there are no additional data to confirm earlier observations on its increasing prevalence. The reported β-lactamase production by *H influenzae* and *M catarrhalis* from acute effusions remains stable at about 10% to 20% and 50% to 80% of strains, respectively. There is some evidence that the percentage of *Streptococcus pneumoniae* susceptibility to trimethoprim-sulfamethoxazole has increased gradually since the introduction of these drugs in the late 1970s. Recent reports suggest that this increased resistance may be a particular problem for children in day-care centers, for whom extensive antibiotic use may select out resistant strains. The contribution of anaerobic bacteria to otitis media is still not clear. There is no new evidence to suggest any more strongly that *Chlamydia trachomatis* is an etiologic agent for acute or chronic otitis. Finally, there is no new information on coagulase-negative staphylococci as pathogens in the evolution of infectious middle ear disease. Additional information in other specific areas is summarized below.

1. *Contribution of Bacterial Cell Envelope Substances to Pathogenesis of Middle Ear Disease.* Significant progress has been made in the immunology of microbial cell wall. The presence of bacterial lipopolysaccharide (endotoxin) has been demonstrated in the middle ear effusions in a significant proportion of patients with otitis media with effusion. Furthermore, purified lipopolysaccharide has been observed to induce extensive inflammatory changes in the middle ear in experimental animals.[3] These studies suggest that endotoxin may be a potential contributor to the development and persistence of effusions in certain children.

The relationship of pneumococcal surface antigens to the pathogenesis of disease is less clear. Pneumococcal cell surface components also invoke inflammation. Pneumococcal cell wall has an inflammatory effect on meningeal and respiratory tissues, and causes acute and chronic middle ear inflammation in the chinchilla otitis media model. The persistence of pneumococcal capsular polysaccharides in middle ear effusions of children with chronic otitis media with effusion for months after an acute pneumococcal otitis media episode suggests that other components (eg, cell wall) also may persist. Recent evidence indicates that immune complexes of pneumococcal capsular polysaccharides and antibody do not contribute to ongoing inflammation or recurrent otitis media.

2. *Contribution of Bacteria to Chronic Otitis Media With Effusion.* The relationship of the bacteria that are found in middle ear effusions in children with chronic disease to the ongoing inflammatory process has not been determined. Some investigators have reported that concentrations of lysozyme, lactoferrin, and chemotaxins were significantly higher in bacterial culture-positive than in sterile effusions. However, the chemotaxin(s) content correlated poorly with the levels of C3 and C5a complement components in the effusions. These findings suggest that bacterial components may contribute to the observed inflammatory activity, and to the evolution of chronic middle ear inflammation.

3. *Nontypeable* H influenzae. Several recent studies have explored the relationship of nontypeable *H influenzae* to otitis media. A few investigators have examined the pharyngeal carriage of *Hemophilus* species in children and adults and demonstrated age-related differences in the carriage rates. Other studies have explored the epidemiology of nasopharyngeal colonization with nontypeable *H influenzae* in small numbers of children and have shown that colonization was a dynamic process, with children gaining and losing several strains over a period of several months. Other investigators have attempted to identify differences between nontypeable *H influenzae* strains that were isolated from middle ear and those isolated from nasopharyngeal specimens. No significant differences were found in the adherence characteristics or biotypes of the "otitis" strains and the "carriage" strains. Additional strain markers, such as isoenzyme patterns, may allow distinction between different nontypeable *H influenzae* strains. These markers have been employed for epidemiologic studies. However, their importance to the relative virulence of different strains has not been explored. A recent study has identified a 16.6-kd outer membrane protein as a specific target of bactericidal antibody, and this protein appears to be common to all *Hemophilus* strains tested to date.

4. *Bacterial Adherence.* Several investigators have begun to focus on bacterial adherence mechanisms to determine how this first step in the pathogenic process is initiated by successful pathogens of the middle ear. Studies have identified a specific disaccharide, N-acetyl glucosamine β1→3 galactose, that appears to be the membrane receptor for *S pneumoniae*.[4] The receptor appears to shed in free form in some external sections such as human milk. Fimbriae have been identified on most freshly isolated nontypeable *H influenzae* strains, but their contribution to adherence is unclear. Understanding the attachment phenomenon, which is mediated by specific bacterial appendages (fimbriae, fibrillae) and host cell receptors, may provide an opportunity for designing effective measures to prevent colonization and subsequent disease with microbial organisms.

SHORT-TERM GOALS

Many of the research goals outlined in the 1983 report remain to be addressed fully and should be the primary focus of continuing studies. Other areas for future studies represent logical extensions of some of the more recent investigations outlined above.

The prevalence of antimicrobial resistance among bacterial species isolated from middle ear effusion should continue to be monitored on a worldwide basis. The prevalence of β-lactamase production by nontypeable *H influenzae* and *M catarrhalis* has been documented in studies from selected areas, but systematic studies of isolates from different regions of the world are not available. Such information has very important implications in the development of rational recommendations for antimicrobial therapy.

The role of coagulase-negative staphylococci, anaerobic organisms, and *C trachomatis* in the pathogenesis of otitis media remains to be defined clearly. Since the last Research Conference, there has been little or no new information published on the relationship of these organisms to otitis media. In particular, further studies in animal models of infection might be appropriate at this time.

The relative role played by various organisms in neonatal otitis media remains to be clearly defined and should be the focus of some future investigations.

The pathogenic potential of endotoxin and other cell wall components in otitis media has been proposed by some of the studies outlined above. Further studies to define which of the many potential inflammatory responses induced by endotoxin or pneumococcal cell wall in middle ear are important to the observed effects would seem appropriate. For example, in the animal model one might explore the effects of endotoxin on the levels of complement components and their breakdown products in middle ear fluid and on the levels of lysosomal proteases, histamine, leukotrienes, and a variety of other potential inflammatory mediators. The effect of various inhibitors, such as aprotinin or α2-macroglobulin, might also be explored in such settings. The observed immunosuppressive effects of middle ear fluid macrophages on the in vitro proliferative responses of lymphocytes may conceivably be related in some way to prior exposure to endotoxin, and this relationship may be useful to explore.

Extensions of some of the studies on viral pathogenesis outlined above should be pursued. The human studies and animals models of infection that suggest ciliated cells are the cells most susceptible to viral damage should be expanded to include studies of other viruses.[2] Functional correlates of the pathologic changes should be explored in animal models or in tissue explants in vitro. Studies on the interactions between viruses and bacteria that contribute to the pathogenesis of disease should be further expanded.

The role played by viable bacteria in the pathogenesis of persistent middle ear effusion and epithelial secretory activity has yet to be defined fully and should continue to be a major priority. Again, animal models of infection will be the most appropriate setting in which to explore these questions.

Bacterial virulence factors for *H influenzae*, *M catarrhalis*, and others should be delineated more clearly. Use of genetic variants may be particularly worthwhile in this regard.

LONG-TERM GOALS

Many long-range goals identified during the previous Conference are still far from being accomplished. Long-term goals of future studies should include efforts to better understand the age-specific host responses to viral and bacterial infections that predispose to acute and chronic otitis media. Other possible goals should include 1) obtaining further information on the contribution of bacterial subcellular components (ie, cell wall, cell membrane) on the pathogenesis of otitis media with effusion; 2) understanding if and how bacteria stimulate the epithelial secretory process and subepithelial reactivity, which is associated with chronic effusions; and 3) understanding why microorganisms persist in chronic otitis media with effusion, and precisely what their role might be in the pathogenesis and evolution of chronic middle ear disease.

IMMUNOLOGY

Since 1983, significant progress has been made in a number of areas of immunology, including the immunology of otitis media. It is becoming increasingly obvious that there is a complex interplay between the mucosal and systemic immune systems directed against a variety of antigens in the middle ear.

IMMUNOLOGIC EVENTS IN OTITIS MEDIA WITH NONTYPEABLE *H INFLUENZAE* IN CHINCHILLA MODEL

Several groups have recently explored interesting approaches concerning host immunity and nontypeable *H influenzae* otitis in chinchillas. It has been reported that experimentally induced otitis in chinchillas leads to the development of strain-specific protective immunity both in the ear that had been challenged previously and in the contralateral ear. This latter observation is in contrast to previous observations with experimentally induced pneumococcal otitis media, which suggested that protective immunity was restricted to the ear that had been infected previously. The development of protective immunity was associated with a concomitant serologic response to outer membrane proteins. Animals remained susceptible to challenge with heterologous strains. Recently, other workers have characterized the serum and middle ear antibody responses of chinchillas with experimentally induced disease. These data have demonstrated the development of serum and middle ear antibody in convalescent samples and the presence of plasma cells in the mucosa of the middle ear 2 weeks after infection. It has been suggested that passive immunization with specific immune serum can protect chinchillas against experimental challenge with homologous nontypeable *H influenzae* strains. The protective immune serum contained antibodies against both bacterial outer membrane proteins and lipopolysaccharide. These observations suggest that antibodies present in the serum may partly mediate protection, without the requirement for locally produced antibody within the middle ear space.

Several workers have been able to produce middle ear effusions in experimental animals by immunizing animals intradermally with keyhole limpet hemocyanin and several weeks later challenging them locally with the same antigen. Effusions thus induced were associated with extensive inflammatory cellular infiltration, but did not result in eustachian tube dysfunction. Recently, the effects of complement depletion on the middle ear inflammation induced by secondary antigenic challenge also have been studied. Although complement-depleted animals demonstrated some decrease in inflammation and effusion, a substantial reaction still was observed. Thus, in such models of inflammatory otitis media, factors other than complement must contribute to the observed disease.

Antigenic challenge to the tympanic cavity in systemically sensitized animals has been shown to induce an effusion and distinct inflammatory changes in the middle ear mucosa. Animals in which otitis media is induced in such a manner must have high circulating immunoglobulin (Ig) G antibody titers against the antigen. Recent studies also have presented evidence that important regulatory interactions take place between the systemic and mucosal immune systems. For example, in animal models, oral introduction of antigens has been shown to induce systemic hyporesponsiveness (oral tolerance) to subsequent parenteral injection of the same antigen, without influencing the production of IgA antibodies in the gut and at sites distant from the gut, such as in colostral, lacrimal, and salivary secretions and middle ear. It has been observed that immune-mediated otitis media is suppressed by oral administration of antigen in guinea pigs. The transfer of antigen-specific suppressor T-cells from the gut-associated lymphoid tissue suppresses the induction of immune-mediated otitis media with effusion in mice. It also was shown that the induction of antigen-specific IgA-forming cells occurs in the mucosal lining of the nasopharynx and eustachian tube.

Although IgE-mediated allergy does not appear to be a direct causative factor in the production of middle ear effusions, nasal allergy appears to be a factor in the proneness to and recurrence of otitis media with effusion. It thus is suggested that induced nasal allergic reactions can result in tubal dysfunction in guinea pigs. Animals passively sensitized by intravenous injection of antidinitrophenyl IgE antibody serum, and challenged by intranasal introduction of dinitrophenyl-ovalbumin, developed typical type I allergic reactions in the mucosa covering the nasopharynx and eustachian tube.

CLINICAL OBSERVATIONS: IMMUNOREGULATORY DEFECTS IN CHILDREN WITH OTITIS MEDIA

Several studies have described a variety of humoral and cellular defects in children with otitis media.

One area that is beginning to be explored is the possible relationship between immunoglobulin subclass deficiencies and susceptibility to recurrent otitis media. Antibodies to pneumococcal phosphorylcholine, a cell wall component, were found to exhibit restriction to IgG subclasses. Earlier studies have been followed up with subsequent experiments that suggest that otitis-prone children have significantly lower serum IgG2 levels than appropriate controls. Patients with the lowest IgG2 levels appeared to be more susceptible to nontypeable *H influenzae* infections than those with normal immunoglobulin levels.

In other studies, it has been reported that children with recurrent otitis media have lower serum IgG and IgA activity against pneumococcal serotypes associated with otitis media than observed in control children without any history of disease.

One recent report has examined the relationship between immunoglobulin allotype markers and risk of recurrent otitis media. This study was prompted by earlier studies in adults, which suggested that the antibody responses to pneumococcal polysaccharide antigens were controlled by genes linked with those for the Km and G2m allotypic markers. However, in other reports, the distribution of Gm and Km markers between children with recurrent otitis media and healthy controls was not statistically different. These latter results have been confirmed recently. It appears from one recent study that the otitis-prone children exhibit lower antibody responses following rubella vaccination than do the non–otitis-prone children, indicating that poor responses in such subjects may be directed against other protein antigens.

Cellular immune defects also have been described in patients with chronic otitis media with effusion. Some children with otitis media with effusion have exhibited reversed T4-T8 lymphocyte ratios and deficient production of interleukin 2 by peripheral blood lymphocytes. These abnormalities appear to be the result, rather than the cause, of the middle ear disease, since such abnormalities resolved after adequate treatment of the underlying disease.

MIDDLE EAR MACROPHAGES AND LYMPHOCYTES

A number of investigators have characterized the cellular elements in the middle ear fluid of patients with otitis media with effusion. It has been suggested that middle ear fluid macrophages exert a suppressive effect on in vitro immunoglobulin synthesis and lymphocyte proliferation. This effect was thought to be mediated by a 50-kd soluble cytokine. These experiments have been expanded recently in an animal model. Preliminary work was reported in which the lymphocyte subpopulations were characterized. T cells appeared to predominate in all types of effusions with variable ratios of T4 and T8 cells depending on the type of effusion being characterized. In children with recurrent acute otitis media, significantly greater amounts of immature B cells (bearing surface markers CD-19, CD-20, CD-22, and CD-24) were found when compared to non–otitis-prone children. The precise role of such immunoregulatory alterations in the pathogenesis of middle ear disease remains to be defined.

COMPLEMENT PROTEINS IN MIDDLE EAR FLUID

A series of earlier studies examined the middle ear fluid and serum of patients with otitis media for the presence of complement proteins and their breakdown products. These studies have been extended recently. Middle ear fluid from children with serous otitis media has been examined for the presence of C3 breakdown products and for the presence of C3 splitting activity. These studies have suggested the absence of hemolytic complement activity in most middle ear effusions, substantial levels of C3 breakdown products, and C3 splitting activity that appears to be mediated by antibody-independent mechanisms. Other studies have documented the presence of alternative complement pathway components in middle ear effusions. However, most investigations to date have been unable to correlate the levels of complement proteins with the presence or the severity of disease.

ANTIBODIES IN MIDDLE EAR AND NASOPHARYNGEAL FLUIDS

Significantly lower levels of secretory IgM are present in nasopharyngeal secretions of children with recurrent acute otitis media compared with healthy children. Moreover, recent findings indicate that during the very early phase of acute otitis media, pathogen-specific antibodies appear in the middle ear effusion, primarily by transudation from the serum.

SHORT-TERM GOALS

Our understanding of host immunity and its relationship to protection against bacterial middle ear disease remains rudimentary. Further studies in animal models to define those components of the host immune response that are necessary and that may be sufficient to protect against experimentally induced pneumococcal or *Hemophilus* disease should be pursued.

The intriguing studies that suggest a relationship between antibody subclass deficiencies and risk of otitis media must be pursued. Additional studies of the response of children with recurrent otitis to immunization with polysaccharide vaccines should be pursued, perhaps focusing on older children and different serotypes than those examined previously.

The relationship between the observed alterations in macrophage function, lymphocyte populations, and complement components and the pathogenesis of disease remains unclear at present. Studies to explore these alterations further should be pursued, perhaps with a major emphasis on animal models. Experimental manipulations designed to alter individual parameters in such models may allow us to define more clearly which abnormalities are the cause and which are the result of middle ear inflammation.

Little information is available concerning the role of therapeutic modulation of otitis media with effusion or the development of specific immune response. The role of antibiotics in either directly or indirectly depressing an immune response needs to be defined more clearly. Investigations both in animal models and in humans might be considered in approaching this issue.

Finally, it will be desirable to identify the source of lymphocytes in the upper respiratory tract and the middle ear mucosa. Do tonsils and adenoids serve as a source of precursor cells for the middle ear during otitis media with effusion?

LONG-TERM GOALS

Many of the long-range goals stated in the 1983 report are still very applicable today. It is hoped that as we are able to gain a clearer understanding of how the various immunologic parameters contribute to the pathogenesis of or recovery from disease, we will be able to manipulate individual components for the benefit of the host by pharmacologic or immunologic means.

As stated in the previous report, it would be extremely valuable if we were able to better understand the cell trafficking of immunocompetent cells that reach the middle ear mucosa. Such information may be helpful in developing successful vaccination strategies for the prevention of disease. It may be that studies will need to be carried out in primates, or perhaps only in humans, if they are going to have relevance to the protection of young children.

More information is needed about the following areas: 1) the maturation of the middle ear mucosa to the immune active stage, 2) the protective and the predisposing mechanisms of systemic and local immune responses during otitis media, 3) the development of bacterial and viral antigen-specific humoral immune mechanisms, 4) the specific and nonspecific cellular immune response during otitis media, and 5) the protective or possible harmful role of the substances secreted by the inflammatory cells in the middle ear mucosa during acute infections.

BIOCHEMISTRY

Many advances in the biochemical characterization of middle ear effusion and mucosal chemistry have been made in several areas, through the study of both humans with natural disease and animals with experimentally induced otitis media.

PROTEINS AND ENZYMES

Hydrolase activity has been reported in middle ear effusions from patients with acute otitis media.[5] Substantial levels of a variety of different hydrolases are present in both serous and purulent effusions, but their levels do not appear to be significantly different in different types of effusions. However, bacterial culture-positive effusions have higher levels than culture-negative effusions. The previously noted association between neuraminidase activity and positive pneumococcal cultures has been confirmed in more recent studies.

Increased levels of various hydrolytic enzymes have been demonstrated in chinchillas experimentally inoculated with various microorganisms. It has been shown that specific increases in hydrolase activity occur that are characteristic of infection with a particular microorganism. Thus it may be possible to determine the causative organism in acute otitis media from the activity profile in different effusions.

The kallikrein-kinin system in middle ear effusions has been examined in some studies. Prekallikrein appears to be present in both serous and mucoid effusions. Kallikrein hydrolytic activity has been detected in different types of middle ear effusions, although the activity appears to be somewhat higher in serous effusions. The substrate kininogen is found only in serous effusions. These data suggest that the kallikrein-kinin system may be related to the pathogenesis of middle ear fluid accumulation, especially in patients with serous otitis. However, in mucoid effusions, the absence of kininogen, perhaps due to previous activation, likely would prevent the production of active bradykinin, which is involved in vascular permeability.

The effects of neuraminidase on the middle ear mucosa have been explored in experimentally inoculated chinchillas.[6] These studies have demonstrated that neuraminidase may lead to the exposure of galactose residues in mucosal glycoproteins, presumably secondary to removal of terminal sialic acid residues. It has been suggested that such membrane destruction may contribute significantly to the pathologic effects of otitis media with effusion.

Demonstration of the relationship between the inflammatory cell components and the biochemical profile of the effusions has been reported.[7] Sequential cytology of both purulent otitis media and secretory otitis media has been correlated with lysozyme levels in the effusions. Neutrophil counts reach higher levels and peak earlier in purulent than in serous otitis media. Lysozyme level was correlated with total inflammatory cell counts. It was concluded that lysozyme is produced locally, because the middle ear effusion level was much greater than the serum level, and that the major source is the inflammatory cells (neutrophils and macrophages). However, the sources of other enzymes in middle ear effusion are not yet delineated clearly.

CARBOHYDRATE COMPOSITION AND RHEOLOGIC PROPERTIES OF MIDDLE EAR EFFUSION AND MUCUS

Since the 1983 Symposium, limited additional information has become available in this area. The middle ear mucins from patients with middle ear effusion have been characterized recently. The amino acid and carbohydrate compositions of middle ear mucins appear to be similar to those reported previously for other epithelial mucins. Variations, however, are apparent when mucins from different types of middle ear fluids are analyzed. Carbohydrate content is lowest in mucins from purulent effusions and mucoid effusions from children with cleft palate. The carbohydrate content can be correlated with the rheologic activity of reconstituted mucins. Additionally, transport studies indicate that certain middle ear effusions such as those from patients with cleft palate may not be cleared efficiently because of insufficient viscoelasticity.

Both elasticity and viscosity of middle ear effusion have been determined and compared with transportability of the middle ear effusion on the mucus-depleted palate of the frog. There is a sharp increase in transport with increase in elasticity up to 20 dyne/cm^2 and in viscosity up to 2 poise. There is a slow decrease in transport with increasing elasticity and viscosity at the higher values of 20 dyne/cm^2 and 2 poise, respectively. Further investigations are clearly necessary to understand the clinical importance of the relation of mucociliary clearance to the rheologic properties of middle ear effusion.

INFLAMMATORY MEDIATORS

The involvement of histamine in the pathogenesis of otitis media is conceivable, since various stimuli in the course of infection can induce its production. Histamine has been demonstrated in both mucoid and serous effusions at levels greater than those in serum. Injection of histamine into the middle ear cavity has been found to result in marked mucosal edema and effusions that persist for several hours. Specific histamine inhibitors were able to partially, but not completely, block the observed changes. The sources and role of histamine in middle ear effusion have not been defined clearly.

Progress has been made in the study of the role of arachidonic acid metabolites in the pathogenesis of otitis media.[8] Levels of prostaglandins (PGs) and other arachidonic acid metabolites in the human middle ear effusion were measured and analyzed according to the age group. In general, levels of PGE2 and 6-keto-PGH1α were higher in the younger age group (0 to 5 years of age) than the older age group (10 to 15 years of age). For the first time, concentrations of lipoxygenase products including 5-hydroxyeicosatetraenoic acid, 15-hydroxyeicosatetraenoic acid, leukotriene (LT) B4, and LTC4 in human middle ear effusion have been reported. Sequential changes in the levels of PGs and LTs in the animal models of otitis media also have been examined. Levels of LTB4 in bacterial culture-positive middle ear effusion were higher than in the culture-negative groups. Leukotriene B4 appears to be another marker for the presence of bacteria and inflammation in otitis media. One recent investigation has provided strong evidence of eustachian tube dysfunction as a result of release of LTC4 in upper airway during natural exposure to environmental allergens such as ragweed. The role of arachidonic acid metabolites in the pathogenesis of various types of otitis media needs to be investigated further.

PROTEASES AND PROTEASE INHIBITORS

Lysosomal enzymes in middle ear effusion may play a significant role in the induction or maintenance of inflammation in the middle ear and the chronicity of otitis media with effusion. Inflammatory cells in middle ear effusion, especially neutrophils and macrophages, contain various potent proteolytic enzymes. If not inactivated by protease inhibitors promptly, these enzymes may cause tissue damage.

Activities of cathepsin B and H in middle ear effusion have been found to be significantly higher than in plasma.[9] Cathepsin B activity in mucoid middle ear effusion appears to be higher than that in serous effusions. The activity of trypsinlike proteases is found to be low in both middle ear effusion and plasma.

Middle ear effusion collected from adult patients with otitis media with effusion contains large amounts of unsaturated alpha protease inhibitor, mainly α1-antitrypsin, and the hydrolytic activity of trypsinlike protease is generally low. On the other hand, lysosomal thiol proteases (such as cathepsin B) appear to be the major proteolytic enzymes in middle ear effusion of otitis media with effusion in childhood, possibly because of the shortage of thiol protease–specific inhibitors. Hydrolytic activity of cathepsin B–like thiol proteases and collagenolytic proteases has been measured in middle ear effusion from pediatric patients with acute and chronic otitis media with effusion. Both activities are significantly higher in middle ear effusion from acute than in chronic forms of otitis media with effusion. Collagenolytic proteases in acute otitis media with effusion seem to be much more active than in chronic otitis media with effusion. The presence of large amounts of unsaturated alpha-protease inhibitor in middle ear effusion may indicate that proteolytic function of serine proteases (elastase, cathepsin G) is not as important as lysosomal thiol proteases. The shortage of thiol protease inhibitor (α2-macroglobulin) could indicate long-lasting retention of free thiol proteases, mainly cathepsin B from macrophage. Therefore, thiol proteases may have a major proteolytic function in middle ear effusion and could be related to the pathogenesis of chronic otitis media with effusion.

EFFECTS OF MEDICAL TREATMENT ON BIOCHEMICAL COMPONENTS OF MIDDLE EAR EFFUSION

Ampicillin treatment of chinchillas with *S pneumoniae*- or *H influenzae*-induced otitis media with effusion has been shown to decrease the levels of hydrolytic enzymes found in middle ear effusion, thus suggesting that early antimicrobial therapy may be of significant benefit. In addition to reported effects of systemic treatment of otitis media, local treatment with steroids or other anti-inflammatory agents proved to be effective in the suppression of inflammatory changes in experimental otitis media. Further evaluation of the efficacy of both systemic and local treatments is necessary.

SHORT-TERM GOALS

1. Establishment and evaluation of selective biochemical markers (proteins, enzymes, arachidonic acid metabolites, carbohydrates, protease inhibitors, rheologic properties) for better understanding of inflammatory reaction in the middle ear cavity in various types of otitis media.

2. Investigation of the relationship between clinical findings, biochemical markers, and other markers of disease such as immunologic determinants and morphologic parameters.

3. Investigation of the application of biochemical and immunologic markers to the evaluation of efficacy of various treatments.

4. Development of techniques for the liquefaction of mucoid effusions.

5. Development of new standardized micromethods for various biochemical markers.

LONG-TERM GOALS

1. Differentiation of the types and stages of inflammation in the middle ear cavity by biochemical markers. It is important to study the parameters collectively and seek correlations between various biochemical parameters and clinical features, together with immunologic and cytologic parameters.

2. Identification of the relationship between biochemical markers, clinical diagnosis, and outcome of disease process in otitis media.

3. Development of new management schemes for otitis media based on the results of efficacy studies using biochemical markers.

VACCINATION

Prevention of otitis media with effusion through prophylaxis with microbial vaccines is potentially one of the most important areas for investigation. Unfortunately, despite significant efforts, progress in the area has been very slow.

PNEUMOCOCCAL VACCINATION

Studies published since the 1983 Symposium have confirmed the lack of significant protection in young children vaccinated with the current pneumococcal vaccines. Field trials carried out in Finland, Sweden, and the United States on the efficacy of polyvalent pneumococcal polysaccharides have shown that although frequency of acute otitis media may be reduced by the use of pneumococcal vaccine, the overall clinical efficacy of the currently available vaccine to prevent acute otitis media is at best minimal in young children. In studies of vaccines in over 4,000 infants and children, the protective efficacy of the vaccine was negligible among children younger than 2 years, although a significant pneumococcal type-specific protection was observed for the most immunogenic polysaccharide types. Among older children there was about a 10% reduction of acute otitis media episodes during the first 6 months after vaccination. The efficacy was not affected by the number or the microbial origin of acute otitis attacks before vaccination. The protective effects of the vaccine correlated with the immunogenicity of the polysaccharides present in the vaccine and was generally poor among infants, especially to the pneumococcal types most prevalent in acute otitis media in infants.

Antibody responses improved with age, and the improvement varied with the individual polysaccharides. Thus, pneumococcal polysaccharide vaccines may be of some value in children 2 years or older who have recurrent attacks of acute otitis media. However, even among this group the protection must be considered incomplete. In general, young children, especially those under the age of 2 years, fail to respond immunologically to a number of bacterial polysaccharide antigens. Maximum attack rates of pneumococcal infection, including otitis media and bacteremia, occur between the ages of 6 months and 2 years.

Initial immunologic responses to vaccination with pneumococcal polysaccharides in infancy are predominantly of the IgM class, and the protection afforded by such antibodies may be of limited duration, usually not exceeding 6 months. The ability to respond to different pneumococcal capsular polysaccharides develops at different ages; for example, immunity to type 3 capsular polysaccharide is observed as early as 6 months of age. Responsiveness to the serotypes responsible for the majority of infections in early life (types 6A, 6B, 14, 19F, 19A, and 23F) may be delayed until the age of 4 years or later. Although treatment with antibiotics such as penicillin has greatly reduced the morbidity and mortality of established pneumococcal infections, the continued emergence of antibiotic-resistant strains further emphasizes the need for the development of vaccines that can provide long-term protection against the organism.

Effective and practical vaccination against pneumococcal otitis media in children, and pneumococcal pneumonia in children and high-risk adults, still awaits the development of vaccines that are more immunogenic. Because young children fail to respond immunologically to a number of bacterial polysaccharide antigens, vaccines with increased immunogenicity will be needed to provide protection to those under 4 years of age. Such vaccines might also benefit subjects who have impaired immune responses and who could not normally respond to the conventional vaccine. Vaccines employing combinations of protein-polysaccharide conjugates currently are being studied as one possible approach to these problems.

H INFLUENZAE VACCINES

The failure of antimicrobial agents to prevent a significant residue of mortality from nontypeable *H influenzae* infections of the lower respiratory tract, the importance of nontypeable *H influenzae* as a cause of otitis media, and the continued emergence of antibiotic-resistant nontypeable *H influenzae* strains all indicate the need for the development of a vaccine to prevent disease caused by nontypeable *H influenzae*. The fact that systemic immunization with capsular polysaccharides of *S pneumoniae* has been able to prevent pneumococcal pneumonia in humans and protect against otitis media in an animal model system suggests that systemic immunization against nontypeable *H influenzae* also might be able to protect against both pneumonia and otitis media caused by this organism.

Several advances have been made that may have relevance to prevention of otitis media with effusion. Recent studies have characterized the antigens from representative nontypeable *H influenzae* isolates that are recognized by human bactericidal antibodies. It appears that bacterial outer membrane proteins, as opposed to lipopolysaccharide, are the principal targets of bactericidal antibody in the serum. Furthermore, antibody to the 16.5-kd protein has been observed in sera from patients recovering from nontypeable *H influenzae* disease, and the protein appears to be common to all *Hemophilus* strains tested, both type b and nontypeable.

Pilus vaccines for otitis media and other diseases caused by *H influenzae*, both typeable and nontypeable, are currently under development. Pili are virulence and immunity determinants in the chinchilla model of otitis media. Low doses (ten colony-forming units) of either piliated or nonpiliated phases of *H influenzae* will cause colonization and middle ear disease when inoculated in the middle ear or the nasopharynx. Pilus immunization of chinchillas has been shown to lead to effective clearance of piliated phase *H influenzae* from the nasopharynx and the middle ear. In the intrabullar model, pilus immunization protected against colonization and effusion to piliated phase inoculum. Such immunization also protected against colonization and effusion on subsequent challenge with either piliated or nonpiliated phases in the intranasal challenge model. Interestingly, nasopharyngeal colonization was reduced rapidly by pilus immunization. These observations suggest that pilus vaccine potentially could eradicate *H influenzae* from its human nasopharyngeal reservoir.

Protection by pilus immunization has been found to be pilus type–specific. Although pilus typing has not been completed so far, five pilus types covering about 97% of pili from known piliated strains have been identified. Based on these findings, it is possible that a multivalent pilus vaccine having a reasonably limited number of types may be available in the future.

POLYSACCHARIDE-PROTEIN CONJUGATE VACCINES

Conjugate vaccines have been developed by linking polysaccharide antigens covalently to protein carriers. The relevant experience to date has been with *H influenzae* type b polysaccharide-protein conjugates. Efficacy trials in infants using a conjugate *H influenzae* type b vaccine are in progress in a high-risk native infant population in Alaska and in all newborns in Finland. No efficacy data are available at this time from the trial in Alaska, whereas data from the Finnish trial suggest some efficacy. Most immunogenicity data with the conjugated vaccines were obtained from experiments with animal models, college students, and normal children. These data suggest that the conjugates may be better immunogens than capsular polysaccharide alone and may produce antibody that has a longer duration. Data from a rat model further indicate that the immune response is mature, and that an isotype switch to IgG is seen, rather than the isotype-restricted response seen following immunization with the plain polysaccharide antigens.

Chemical conjugation of pneumococcal capsular antigens to proteins such as diphtheria or tetanus toxoid has been shown to alter their immunogenicity by converting the polysaccharide from a T cell–independent to a T cell–dependent antigen. A vaccine to type 6A pneumococcus conjugated with tetanus toxoid has been shown to be both immunogenic and relatively safe in rhesus monkeys and in a small number of children and adults. Preliminary studies with this conjugate vaccine suggest that responsiveness to the conjugated capsular polysaccharide antigen occurs at a significantly earlier age and induces both IgM and IgG antibodies.

Final recommendations on the general use of conjugate vaccines for diseases produced by encapsulated and nonencapsulated bacteria and perhaps other diseases as well will have to await the completion of efficacy trials now in progress. Additional data also are required to establish the incidence of reactions to and the relative safety of conjugated capsular polysaccharides.

VIRAL VACCINES

Safe and effective vaccines against respiratory viruses are not currently available, with the possible exception of influenza A and B viruses. Clinical trials have been initiated recently with live attenuated vaccines for respiratory syncytial, influenza, and parainfluenza viruses. The attenuated strains are cold-adapted, temperature-sensitive mutants, or genetic reassortants. Although data on clinical efficacy against diseases in susceptible population groups are modest at best, modification of these approaches involving the use of viral glycoprotein-specific vaccines is currently in progress. Success in these approaches with viral immunization will have great impact on child health. The potential for reducing the incidence or severity of viral-associated otitis media by such immunization, however, cannot be predicted at this time.

IMMUNOGLOBULIN PROPHYLAXIS

The effect of immunoglobulin treatment has been investigated in some Swedish studies. Although regular periodic administration of large doses caused transitory increases in IgG antibody activity in two independent trials, clinical protection of young otitis-prone children from further attacks of otitis was not achieved. A human hyperimmune globulin termed bacterial polysaccharide immune globulin has been prepared from the pooled plasma of donors immunized with polyvalent pneumococcal, meningococcal and *H influenzae* type b vaccines. A recently completed study examined the effects of bacterial polysaccharide immune globulin on the frequency of *H influenzae* type b infections and colonizations in Apache infants. A significant reduction in bacteremic *H influenzae* type b infections, as well as a reduction in detectable *H influenzae* type b colonization, was noted. Pneumococcal bacteremias also were reduced, but the numbers were too small to reach statistical significance. Studies are now in progress to determine the effect of bacterial polysaccharide immune globulin therapy in the prevention of acute otitis media in young, high-risk children.

As pointed out earlier, several prevalent serotypes of *S pneumoniae* are poorly immunogenic in young infants. Passive immunization with bacterial polysaccharide immune globulin may provide a broader range of effects than that provided by even the most optimal response to purified pneumococcal capsular polysaccharides. Unencapsulated strains of *H influenzae* and *M catarrhalis* are each isolated from a large percentage of infants with acute otitis media. Antibodies to these organisms are present in the sera of most normal adults and presumably in bacterial polysaccharide immune globulin. Thus bacterial polysaccharide immune globulin may provide a greater effect than pneumococcal vaccine on overall otitis media morbidity, if its protective activity includes such nonspecific type infections. Passive immunoprophylaxis also may be potentially effective in patients who may fail to respond to improved vaccines developed in the future.

SHORT-TERM GOALS

The goals in this area continue to be much the same as stated in the previous report. Research and development of improved pneumococcal vaccines should be continued. Studies on their safety, immunogenicity, efficacy, and specificity in experimental animals and, if successful, in infants should be encouraged. The development of vaccines against nontypeable *H influenzae* outer membrane protein also should be continued and their possible usefulness similarly tested. Because protection against acute otitis media seems to correlate with homotypic serum antibody responses, good systemic immunogenicity of the vaccines in infants should be proven before clinical efficacy trials.

LONG-TERM GOALS

Studies of the protective role of viral vaccines and identification of relevant protective viral epitopes or antigens in the variety of viruses associated with middle ear disease are major long-term goals. To cover all the major pathogens of acute otitis media, the eventual goal should be to develop vaccine(s) effective against *S pneumoniae*, nontypeable *H influenzae*, and *M catarrhalis*. Approaches such as conjugating the polysaccharide antigens or other antigenic protein components to other useful carrier proteins, development of recombinant subunit vaccines, and/or development of synthetic microbial subunits also must be considered. In view of the recent encouraging experience with synthetic peptides as effective immunogens against *Vibrio cholerae*, influenza virus, and certain protozoic antigens, this approach may hold considerable promise of developing effective immunization procedures for respiratory pathogens associated with otitis media.

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5. ANIMAL MODELS OF OTITIS MEDIA

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INTRODUCTION

In many instances, significant advances in the treatment of human disease have resulted from the use of animal models. They permit investigations that would be difficult, if not impossible, to perform on human patients. The ability to introduce pathogens and radiolabeled or otherwise potentially hazardous materials is a major advantage of animal models. However, from a scientific standpoint their most attractive feature is the degree of control that the investigator can exert over the subjects and the disease process. This is especially important in a condition such as otitis media, which has a variable course and uncertain cause. Animal models allow the study of putative etiologic factors in isolation. They also permit the investigator to control the time course of the disease, and to obtain sequential anatomic and biochemical samples.

Animal models have proven to be extremely valuable in addressing a variety of questions related to otitis media with effusion. Studies of the anatomy, biochemistry, and immunology of the inner ear, middle ear, and eustachian tube have been performed both in normal animals and in those with experimentally induced disease. Studies of the physiologic functioning of the middle ear and eustachian tube also have been performed in a wide variety of experimental animals. The use of brain stem evoked audiometry has permitted the evaluation of middle and inner ear function during experimental otitis media with effusion.

RECENT ADVANCES

Recent advances have been made in many areas, some of which were identified in the 1983 Research Conference report as questions that should be the focus of immediate work.

MICROBIOLOGY

1. *Viruses.* The mechanisms by which viral infection may predispose to bacterial otitis media with effusion were examined by Giebink and Wright[1] and Giebink et al.[2] They extended their earlier studies examining the effects of viral infection on leukocyte function and middle ear pressure by examining the virulence of different influenza A strains in the chinchilla model. They demonstrated that the ability of certain viruses (eg, influenza A) to cause disease may relate to their capacity to induce negative middle ear pressure, polymorphonuclear leukocyte dysfunction, and alteration of the mucosal clearance of infecting bacteria. Significant viral strain variation was demonstrated in this work.

2. *Bacterial Cell Envelope Substances.* One of the research goals at the 1983 Conference was to define the extent to which bacterial cell-envelope substances may contribute to the development and persistence of middle ear effusions. The inflammatory potential of lipopolysaccharide from *Hemophilus influenzae* was examined by two groups. Purified lipopolysaccharide, from both type b and nontypeable *Hemophilus*, was capable of inducing extensive inflammatory changes in the middle ear of experimental animals injected with the material.[3,4] These studies suggest that endotoxin may be a major contributor to the development and persistence of effusions in certain children.

3. *Models of Chronic Otitis Media With Effusion.* A wide variety of animal models of middle ear infection have been described over the years. Since the last Symposium, Fulghum et al[5,6] have published a series of articles describing their use of a gerbil model of otitis media for the study of pneumococcal and *Hemophilus* disease. This model should be useful for future investigations, although it is not clear that it has major advantages when compared with previously described models. Grote and van Blitterswijk[7] described their use of the rat model for the study of disease caused by *Staphylococcus aureus.* Since the pathologic findings described were similar to those observed in humans with acute otitis media, this might be a useful model for future work.

4. *Models of Silent Otitis Media.* The contribution of so-called silent otitis media to the late sequelae observed in humans with otitis media has not been well defined. Nevertheless, a series of studies over the years has demonstrated that otitis media on a pathologic basis can exist in the absence

of clinically apparent disease. To further assess this entity, Meyerhoff et al[8] and Giebink et al[9] used the animal model of viral and bacterial coinfection. These authors demonstrated that significant middle ear histopathology persisted in a subset of animals despite normal otoscopic and/or tympanometric examinations.

IMMUNOLOGY

1. *Nontypeable* H influenzae *Otitis Media.* Several groups recently have reported interesting results concerning host immunity and nontypeable *H influenzae* otitis in chinchillas. Karasic et al[10] reported that experimentally induced otitis in chinchillas led to the development of strain-specific protective immunity both in ears that had been challenged previously and in contralateral ears. This latter observation is in contrast to previous observations with experimentally induced *S pneumoniae* otitis media that suggested that protective immunity was restricted to the ear that had been infected previously. The development of protective immunity was associated with a concomitant serologic response to outer membrane proteins. Animals remained susceptible to challenge with heterologous strains. Yamaguchi et al[11] also recently characterized the serum and middle ear fluid antibody responses of chinchillas with experimentally induced disease. They demonstrated the development of serum and middle ear fluid antibody in convalescent sample and also demonstrated the presence of plasma cells in the mucosa of the middle ear by 2 weeks after infection. The antigenic specificities of the measured antibodies were not defined in this work. Finally, protection by means of passive immunoprophylaxis for acute purulent otitis media has been demonstrated by Shurin et al[12] for pneumococcal otitis media and by Barenkamp[13] for nontypeable *H influenzae.* These experiments demonstrate that antibodies present in the serum can mediate protection without the requirement for locally produced antibody within the middle ear space.

2. *Anaerobic Bacteria.* Thore[14] has continued his investigations of immunity in otitis media with effusion mediated by several anaerobes, using a guinea pig model. He found that *Bacteroides fragilis* produced intense, persistent otitis media with effusion, associated with rising serum titers of specific immunoglobulin (Ig) G and, to a lesser extent, IgM. Little serum IgA was observed. Other anaerobes that caused otitis media with effusion of short duration or failed to produce otitis did not result in serum titers following middle ear inoculation.

3. *Immune-Mediated Otitis Media.* Ryan et al[15-17] have continued their studies of immune-mediated middle ear disease in the guinea pig model. These workers were able to produce middle ear effusions in experimental animals by immunizing them intradermally with keyhole limpet hemocyanin and then challenging them in the middle ear with the same antigen several weeks later. The effusions were associated with extensive inflammatory cell infiltration, but did not appear to be associated with eustachian tube dysfunction. In a later study they explored the effect of complement depletion on the middle ear inflammation induced by secondary antigenic challenge. Although complement-depleted animals demonstrated some decrease in inflammation and effusion, a substantial reaction still was observed. Thus, in their model, inflammatory factors other than complement also must be contributing to the observed reactions. This acute, immune-mediated otitis media with effusion is dominated by IgG, both systemic and locally produced.

Mogi[18] has also developed a model of immune-mediated otitis media with effusion based on keyhole limpet hemocyanin in the chinchilla. In this model, he has observed results similar to those reported by Ryan et al,[19] including a predominance of IgG. He hypothesized that this predominance was due to a lack of sensitized lymphocytes that were committed to IgA. To test this, he immunized guinea pigs first intradermally, and then intraduodenally. After a later middle ear challenge, he found an increase in IgA-producing plasma cells in the submucosa of the eustachian tube at its nasopharyngeal orifice, but none in the middle ear itself. In another study, Kawauchi et al[20] fed mice with ovalbumin to sensitize cells of the gut-associated lymphoid tissue. They then passively sensitized syngeneic mice with Peyer's patch cells from the fed mice. The recipients then were sensitized intraperitoneally with ovalbumin and later challenged in the middle ear. Compared to mice that received Peyer's patch cells from unfed donors, the animals showed reduced systemic response to antigen and reduced middle ear response to challenge. The results suggest that both the systemic and middle ear responses to antigen were modulated by antigen-specific suppressor T cells derived from the mucosa of the gut. These observations provide important evidence of interaction between the middle ear mucosa and mucosae at distant sites.

Ryan et al[21] also have demonstrated that by increasing the persistence of antigen in the middle ear cavity, a chronic middle ear effusion can be generated by immune mechanisms in the absence of bacterial infection. Thus immune-mediated otitis media with effusion is not a self-limiting phenomenon. This supports the hypothesis that some chronic sterile effusions in patients may be mediated by immune response to bacterial antigens persisting after an acute episode of bacterial otitis media with effusion. In this chronic model, local production of specific IgA plays a more important role than in an acute immune response.

4. *Allergy.* Doyle et al[22] have continued their

studies in the rhesus monkey model. They explored the contribution of an allergic reaction in the middle ear to the development of otitis media by challenging animals who were passively sensitized with allergic human serum with nasal or eustachian tube pollen challenge. They were unable to demonstrate an inflammatory reaction in the middle ears of such animals. However, earlier studies demonstrated that functional eustachian tube obstruction could be induced by nasal antigenic challenge.[23]

BIOCHEMISTRY

1. *Proteins and Enzymes.* LaMarco et al[24] examined the effects of neuraminidase on the middle ear mucosa of experimentally inoculated chinchillas. These workers were able to demonstrate that neuraminidase incubation led to the exposure of galactose residues on mucosal glycoproteins, presumably secondary to removal of terminal sialic acid residues. The authors suggested that such membrane destruction could contribute significantly to the pathologic effects of otitis media with effusion caused by the pneumococcus.

The normal distribution of lysozyme- and lactoferrin-secreting cells in the chinchilla tubotympanum was described by Hanamure and Lim.[25,26]

2. *Inflammatory Mediators.* Boisvert et al[27] investigated the effects of histamine injection in their animal model of noninfectious otitis media with effusion. Middle ear injection of histamine led to marked mucosal edema and effusion that persisted for several hours. Specific inhibitors were able to partially block the observed changes. These results suggest that histamine present in the middle ear space, presumably released by the abundant mast cells present in the tympanic membrane or middle ear mucosa, may contribute to the inflammatory reaction seen in acute otitis media.

3. *Inflammatory Cells.* McGhee et al[28] have developed an animal model for studying the role of macrophages in middle ear effusion with the use of mineral oil and keyhole limpet hemocyanin applied to the middle ear cavity.

Alm et al[29] and Albiin et al[30] have continued to study the role of mast cells in the tympanic membrane and middle ear mucosa in the pathogenesis of otitis media with effusion. They have documented the distribution of these cells, which are abundant in the pars flaccida of the tympanic membrane and in the middle ear mucosa in the rat[29] and human.[30] They also have observed that experimental degranulation of mast cells leads to otitis media with effusion.

MIDDLE EAR MUCOSA

Changes in the mucosal epithelium and subepithelium during experimental otitis media have been studied further.[31] In addition, the middle ear mucosal epithelium has been cultured by van Blitterswijk et al.[32] This technique should allow future studies of epithelial differentiation in vitro.

EUSTACHIAN TUBE

1. *Obstructive Otitis Media.* Kuijpers and van der Beek[33,34] have developed a model of obstructive otitis media with effusion in the rat, and compared the results obtained in germ-free and germ-carrying animals. They found that an increase in secretory and ciliated epithelial cells was seen only in the presence of bacterial infection of the middle ear. Their model seems appropriate for the investigation of long-term effects of sterile and nonsterile otitis media with effusion.

Kahn[35] has developed a model of functional eustachian tube obstruction leading to otitis media with effusion in the guinea pig. He observed that while infection was a long-term consequence of obstruction, a sterile otitis media with effusion was obtained for a period of several weeks in most animals.

2. *Eustachian Tube Pharmacology.* Pharmacologic studies of eustachian tube function have been performed by two groups. Malm and White[36] found that isoprenaline facilitated the opening of the eustachian tube. Svane-Knudsen et al[37] reported sympathetic influences upon tubal function.

EFFECTS OF OTITIS MEDIA ON INNER EAR

The question of sensorineural damage due to middle ear infection was examined by Morizono et al.[38] Chinchillas were infected with *Streptococcus pneumoniae*, were allowed to develop otitis media with effusion, and then were treated with penicillin to resolve the infection. The finding of significant high-tone hearing losses in about one third of these animals, even though the middle ear conductive apparatus appeared normal, suggests sensorineural lesions.

Sensorineural hearing loss associated with otitis media with effusion could be caused by inflammatory substances passing into the inner ear, perhaps via the round window membrane. Antibody and antigen entering the inner ear could generate immune-mediated inflammation. Passage of antibody from the middle to the inner ear was examined in a guinea pig model by Harris et al,[39,40] who found substantial increases in perilymph antibody levels.

INNERVATION OF MIDDLE EAR CAVITY

Eden and Gannon[41] have extended their studies of neural connections in the tympanic cavity. They have documented an afferent innervation of the middle ear, as well as efferent connections to the eustachian tube musculature. They have proposed a system of reflex control of middle ear ventilation, based on the presence of chemoreceptors and/or baroreceptors in the tympanic cavity, and a reflex arc in the brain stem to the tubal muscles. They also have hypothesized that immaturity of this reflex could contribute to the pathogenesis of otitis media with effusion in children.

CHOLESTEATOMA

Work has continued on an animal model of cholesteatoma. McGinn et al[42] have demonstrated that cholesteatoma cannot be induced surgically in most species, making the gerbil the most appropriate animal model. Macri and Chole[43] have shown that implanted barriers can alter bone resorption in experimental cholesteatoma, and Chole and Tinling[44] have shown that repeated basal lamina breaks are observed in the development of spontaneous cholesteatoma. Most recently, Wolfman and Chole[45] have established a model of retraction pocket cholesteatoma.

IMMEDIATE RESEARCH GOALS

Several of the research goals outlined in the 1983 Conference report remain to be addressed fully and should be the focus of continuing study. Other short-term goals for consideration include natural extensions of the recent investigations outlined above, or address differences between existing animal models and human disease. The following goals have been set for the immediate future.

1. There are a number of ways in which existing animal models of otitis media differ from the various types of otitis media with effusion observed in patients. Development of animal models to match these human conditions more closely should be continued. In particular, models of mucoid otitis media with effusion are lacking in most animal species. Also, models of chronic otitis media with effusion should be developed further. Also, differences between different animal species and humans should be addressed carefully in otitis media with effusion studies. Ignoring major species differences may lead to erroneous conclusions.

2. In research using animal models, the use of a diversity of species should be encouraged to prevent undue influence of individual species characteristics. Animal strains should be defined carefully to ensure replicability among different laboratories.

3. The use of species-appropriate pathogenic organisms should be encouraged. The use of human organisms in animal models is appropriate, since they mediate human disease. However, this technique involves the risk that factors such as failure to replicate or induce symptoms, as is seen in animals infected with some human viruses, may lead to erroneous conclusions.

4. The role of respiratory virus infections in the pathogenesis of acute and chronic otitis media should continue to be explored. Animal models of infection might be used to ask whether ciliary abnormalities similar to those recently reported in humans are observed in experimental infection.[14] Functional correlates of such changes might be explored in animal models or in tissue explants. The effects of viral infection on local and systemic cellular and humoral immune defenses also should be evaluated. The effects of viral infection on the exposure of bacterial surface receptors also would be a fruitful area to explore.

5. The contribution to otitis media with effusion pathogenesis made by bacterial adhesion to nasopharyngeal, eustachian tube, and middle ear epithelial cells is largely unstudied.

6. The role played by viable bacteria in the pathogenesis of chronic inflammation and epithelial secretory activity has yet to be defined fully and should continue to be a research priority. Again, animal models of infection may be the most appropriate setting in which to explore these questions.

7. The pathogenic potential of endotoxin in otitis media has been confirmed by some of the studies listed above. Further experiments to define which of the many potential inflammatory responses induced by endotoxin in the middle ear are central to the observed effects would seem appropriate. For example, in the animal model one might explore the effect of endotoxin injection on the level of complement components and their breakdown products in the middle ear fluid, the level of lysosomal proteases, the level of histamine, and a variety of other potential inflammatory mediators. The effect of various inhibitors such as histamine antagonists or $\alpha 2$-macroglobulin also might be studied in such a setting. The effects of endotoxin on the surface epithelium of the middle ear and tympanic membrane also would be useful to explore. Finally, the effects of endotoxins from different types and strains of bacteria could be evaluated.

8. The operation of immunity in the middle ear needs to be characterized more fully. The source of lymphocytes that populate the middle ear mucosa during immune response should be explored. The relationship between middle ear immune responses and those of other mucosae also should be studied. The participation of lymphocyte subpopulations in middle ear immune responses should be determined with monoclonal antibodies and other markers.

9. Our understanding of host immunity and its relationship to protection against bacterial middle ear disease remains rudimentary. Further studies in animal models to define those components of the host immune response that are necessary and sufficient to protect against experimentally induced pneumococcal or *H influenzae* disease should be pursued.

10. The role of antibiotics in either directly or indirectly depressing an immune response needs to be defined clearly.

11. The effects of inflammatory mediators on middle and inner ear structures is still a largely unexplored area. For example, the role and influence of cytokines in the middle ear has received little attention. Mast cell subpopulations and their mediators should be investigated further.

12. The responses of middle ear blood vessels during otitis media with effusion should be studied. Changes in vascularization and in the permeability of mucosal vessels would be expected.

13. Studies of the middle ear mucosal epithelium in culture should be continued. Factors responsible for transformation from one type of epithelium to another could be investigated in this model. Studies of the subepithelium also should be conducted. These could include characterization of the connective tissue matrix elements.

14. The pathologic events that lead to chronic otitis media with effusion and its sequelae should be investigated by studying biochemical and biophysical components in the fluid phase, as well as the histochemistry of mucoperiosteal tissues.

15. Further attempts to identify biochemical parameters that are predictive of a good or poor clinical outcome in terms of progression to chronic disease are still appropriate. Animal models will be a useful complement to human studies in this area.

16. The effects of otitis media with effusion on inner ear function should be studied further.

17. The effects of otitis media with effusion on tympanic membrane structure and function should be studied further.

18. There are a number of questions regarding the interaction of various etiologic, or potentially etiologic, factors in otitis media with effusion that need to be studied. For example, the relationship observed in human otitis media with effusion patients between alterations in macrophage function, lymphocyte populations, and complement components and the pathogenesis of disease remains unclear at present. In addition, the interaction between bacteria in the middle ear and upper respiratory tract, host response to these microbes, and antimicrobial therapy must be characterized more fully. The relative contribution of serum factors, bacterial products, inflammatory cells, and middle ear mucosa products to the inflammatory reaction present in the middle ear and the interaction of the respective components has yet to be investigated fully. Studies to explore such relationships further can be pursued fruitfully in animal models. Experimental manipulations designed to alter individual parameters in such models may allow us to define more clearly which abnormalities are the cause and which are the result of middle ear inflammation. In this regard, Jung et al[46] have presented promising preliminary data from animal models of interaction between different etiologic factors in otitis media with effusion.

LONG-RANGE RESEARCH GOALS

The long-term goals from the 1983 Conference remain valid.

1. The contributing causes of otitis media will be identified and characterized by the approaches described above, permitting the development of effective strategies to enhance middle ear defense mechanisms so as to promote more rapid resolution of otitis media without sequelae. As basic mechanisms for the pathogenesis of otitis media become understood, clinical trials will be necessary to test hypotheses developed in animal models for their relevance to the human condition.

2. Middle ear events that are associated with inner ear sequelae, such as hearing loss, must be identified in an effort to modify these events and prevent hearing loss.

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6. DIAGNOSIS AND SCREENING

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Patients with otitis media must be identified and the state of their disease categorized by accurate diagnostic techniques before their therapy can be considered. Many patients are prelingual and unable to describe their symptoms; thus, recognition of the disorder depends on accurate examination of well babies, of symptomatic infants and children, and of at-risk groups.

So much has been learned about the natural history and treatment of otitis media since the last Research Conference that the Panel on Diagnosis and Screening is able to make more specific recommendations than were previously possible. The Panel considered diagnosis and screening separately.

DIAGNOSIS

PNEUMOTOSCOPY

Essential for the diagnosis of otitis media is inspection of the tympanic membrane while varying the air pressure in the external auditory canal. This permits judgments to be made of tympanic membrane mobility and middle ear contents that are not possible by simple visualization alone. Pneumotoscopy should be the minimum diagnostic procedure. The examiner can determine if tympanic membrane motion is bidirectional and brisk (normal); in an outward direction only (negative middle ear pressure); or sluggish or absent, as when fluid is present. When it is done with the bright light and magnification of the surgical microscope, even greater definition of the status of the middle ear can be made.

Teaching of pneumotoscopic skills should be part of the training of family physicians, pediatricians, and otolaryngologists. Comparison of pneumotoscopic findings against those of an experienced otoscopist or from tympanometry is essential in the learning process. Validation of pneumotoscopic findings against myringotomy, against tympanometry with established instruments and criteria, or against another validated observer is a requisite for research.

Pneumotoscopy with the otomicroscope should be included in the assessment of patients in research protocols for evaluation of sequelae and, where practical, for diagnosis of effusion as well.

TYMPANOMETRY

The electroacoustic immittance audiometer (tympanometer) provides an objective measure of middle ear pressure and compliance. In the presence of reduced pressure (ie, more negative than -200 mm H_2O) and low compliance, middle ear effusion is likely. For general clinical and research purposes, these two indices are sufficient for the assessment of effusion and may be used in place of more complicated descriptors. In normal infants and children, the acoustic reflex may be absent, and this finding should not be used solely as an indicator of disease.[1] Presence of the acoustic reflex, however, is reassuring of middle ear normality. Several recent publications suggest that measurement of the acoustic reflex with a 660-Hz probe tone is more appropriate in infants and neonates than is the conventional 220-Hz tone.[2-8]

Total reliance upon tympanometry for the diagnosis of otitis media is unwise, as many other conditions may mimic effusion at tympanometry and require pneumotoscopy for complete assessment. Nonetheless, its reliability, objectivity, and ease of use have established the value of tympanometry in the diagnosis of otitis media for both clinical practice and research purposes.

PURE TONE AUDIOMETRY

Detection of otitis media is based on pneumotoscopy and tympanometry, but the determination of functional severity requires knowledge of the degree of hearing loss. Hearing assessment is of clinical utility in making long-term treatment decisions and is necessary for clinical research. In children whose functional age is 3 years or older, behavioral thresholds may be determined readily, and in selected cases, even younger children may be tested reliably.[9] In younger children or in difficult cases, auditory brain stem response audiometry may be used to estimate the auditory thresholds. Knowledge of the degree of hearing loss is important when surgical therapy is being considered, both for therapeutic decision-making and medicolegal considerations.

TYMPANOCENTESIS

In unusual cases, such as those involving a scarred tympanic membrane, diagnosis of effusion may require needle aspiration of the middle ear space (tympanocentesis) or even myringotomy to establish the presence of effusion, the type of effusion, or its microbial content.

SCREENING

Mass screening for otitis media has been the subject of considerable controversy, principally because of ambiguity about specific goals and uncertainty about methodology. Given that many episodes of otitis media resolve or are in the process of treatment, the goals of screening should be the identification of that 10% of cases of otitis media that are truly chronic. Emphasis should be directed toward settings in which early recognition may forestall educational sequelae (as in infants) and those in which recognition of the problem by other means is unlikely (ie, underserved populations).

The 1983 report of this Panel endorsed mass screening as a practical concept. We extend that endorsement by specific recommendations designed to make screening more cost-effective through reduction of the rate of over-referrals and by focusing attention upon high-risk groups.

Since otitis media generally is regarded as a nonlethal disease, screening to identify unrecognized cases should be as specific as possible. The Panel recommends that school screening programs consider the following important factors: age, time of year, pass/fail criteria, laterality, and retesting. Screening for otitis media should include both pure tone audiometry and tympanometry and, ideally, should be integrated with existing programs for detection of hearing loss and speech-language delay. Adequate treatment resources should be available in the community before screening programs are instituted.

SCHOOL SCREENING

1. *Age.* Hearing and middle ear screening should be done in the year of school entry and 1 year later. In most nations, this strategy will survey children in the two ages most likely to have unrecognized effusion: 5- and 6-year-olds. Screening of 7-year-olds and older children is unlikely to identify new cases and is not recommended.[10]

2. *Time of Year.* Hearing and middle ear screening should be done at least biannually, preferably early in the school year and near the end of the school year. This is recommended for two reasons: 1) children with effusion early in the fall are more likely to have chronic cases, probably having persistent effusion over the summer months; and 2) screening during the winter months is likely to detect cases associated with upper respiratory tract infections that usually are either in treatment or are likely to clear as the respiratory illness season passes. Screening in the spring should be reserved for children who were missed earlier or who failed the initial screening.

3. *Pass/Fail Criteria.* Standards for audiometric pass/fail detection of hearing loss generally have been established through existing programs and may vary from locale to locale. Where standards are not established, we recommend that children who are able to detect a 20-dB tone at 1,000 and 2,000 Hz and a 25-dB tone at 4,000 Hz be passed. If desired, audiometric screening may be abbreviated to a single high frequency tone (3,000 or 4,000 Hz), since the vast majority of significant and undetected sensorineural hearing losses involve the high frequencies. Experience indicates that 4 kHz is better than 3 kHz when the intention is to identify high frequency lesions.[11] In addition, high frequency screening is more likely to avoid the problem of background masking noise inherent in low frequency testing.

Tympanometric screening failure is based upon the finding of 1) middle ear pressure more negative than -200 mm H_2O and 2) low compliance. Compliance measures vary with the instrumentation, and standards should be determined locally on the basis of the equipment available. Acoustic reflex measurement should not be a pass/fail criterion in middle ear screening.

4. *Laterality.* Bilateral middle ear screening failure is the key condition being sought and is grounds for an immediate alerting letter or, if associated with failure of auditory screening, a recommendation for assessment by the family's primary care physician at the earliest opportunity. If the child passes the hearing screening, retesting after an appropriate interval is recommended (see below).

A child who has unilateral middle ear screening failure should be rescreened at the next regular time. Two consecutive unilateral failures in the same ear should result in an alerting letter recommending physician assessment at the child's next routine health examination or within 1 year.

5. *Retest.* We recommend a 2-month interval for retesting children with bilateral failures. Children who fail bilaterally at the second examination should receive a letter recommending physician assessment, regardless of the level of hearing. All children who fail, whether unilaterally or bilaterally, should be rescreened at every routine biannual screening examination.

INFANT SCREENING

Those children who develop otitis media during the first year of life are at high risk for repeated episodes and may be at risk for speech and language delay. Therefore, special attention must be paid to detailed pneumotoscopy at well-baby checks in the primary care physician's office and to periodic screening of children in special day-care centers or in government-sponsored Head-Start programs. Such screening should follow the principles enumerated above for school screening. Otoscopic evidence of bilateral effusion in the infant requires prompt physician intervention; in this instance there should be no delay for retesting.

RESEARCH DIRECTIONS

OBJECTIVE TESTING OF INFANTS

Investigation of objective measures to detect otitis media in infants less than 6 months of age should be a continuing goal. At present, there is no clear consensus about the most reliable method. The acoustic reflectometer has received considerable attention regarding its potential as a screening device for otitis media. In the past 4 years, a variety of reports have reviewed its advantages and limitations.[12-14] It should be noted that the device requires little training or skill in its use, but given the continuous range of results, considerable caution must be used in interpretation since no single value may be used as a threshold for the presence or absence of effusion. It is not recommended currently for infants less than 3 months of age. Further research and technologic development are necessary to establish the role of acoustic reflectometry in the screening and clinical practice.

SCREENING FOR SPEECH-LANGUAGE DELAY

Further research is needed for the development of screening devices to detect speech and language delay, particularly in infants under 2 years of age. Validation of existing instruments for children of all ages and development of new, more reliable methods should receive priority.

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7. MANAGEMENT

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Management of otitis media was discussed in the two broad categories of surgical and nonsurgical aspects. Surgical considerations were aural and regional. Nonsurgical therapy encompassed antimicrobials, antihistamines, decongestants, mucolytic agents, anti-inflammatory agents, hyposensitization, and environmental manipulation. Each factor was discussed in relation to acute suppurative otitis media, recurrent acute otitis media with or without persistent middle ear effusions between episodes, and secretory otitis media. Chronic suppurative otitis media was not included in the discussion.

Much clinical and basic science research on otitis media has centered around efficacy of tympanostomy tubes. Tympanostomy tubes are used in children with secretory otitis media as well as in children with recurrent acute suppurative otitis media. With regard to secretory otitis media, most investigators agree that tympanostomy tubes result in immediate auditory benefit. Those authors that detract from the use of tympanostomy tubes suggest that this benefit is no longer present 6 to 9 months following the placement of tympanostomy tubes and that the tympanostomy tubes have the capacity to cause structural damage to the tympanic membrane. An additional problem with the placement of tympanostomy tubes is that of postoperative otorrhea. The role of tympanostomy tubes as a prophylactic means in recurrent acute otitis media is to some extent established[1]; however, a comparison of the relative efficacy as compared to long-term antibiotic treatment and to episodic medical treatment still is needed.

The use of topical nasal decongestants also has been an area of controversy. Although most authors feel that there is a salutary effect from the standpoint of nasal congestion, most authors also agree that there is no proven efficacy as far as improvement of eustachian tube function is concerned.[2,3]

The question regarding the efficacy of adenoidectomy has been argued for many years, and there were conflicting reports. However, two recent well-controlled studies demonstrated a benefit of adenoidectomy in patients with chronic middle ear effusion.[4,5] The role of a deviated nasal septum, especially in the area of the vomeroethmoid suture, in the disturbance of eustachian tube function seems to be a fairly well-accepted fact.[6-9]

Work on systemic antihistamines/decongestants continues. Although not unanimous in their conclusions, most studies show little benefit in the use of these drugs.[10-14] Mucolytic agents have shown promising results in chronic otitis media with effusion in human[15] and experimental animal studies,[16] but further work is needed. Steroid therapy for this indication has given conflicting results.[17,18] A course of antibiotic therapy for chronic otitis media with effusion also has been beneficial, but only in the short term.[19,20]

For treatment of acute purulent otitis media with effusion, several new antibiotics have been evaluated, including erythromycin-sulfisoxazole[21,22] and amoxicillin-clavulanate.[23,24] In comparison with amoxicillin[22,23] or cefaclor,[21,24] they were equally effective.

The duration of therapy for acute otitis media with effusion has been evaluated in several studies. Ingvarsson and Lundgren[25] and Hendrickse et al[26] found similar success rates with 5 days of therapy compared with the traditional 10 days. Meistrup-Larsen et al[27] have reported that 2 days of therapy with penicillin V is as effective as 7 days. Van Buchem et al[28] and Ostfeld et al[29] have reported successful management of acute otitis media with effusion without antibiotic therapy. Certain flaws of design in some of those studies make them difficult to interpret.

GENERAL STATEMENT REGARDING FUTURE RESEARCH

Results of clinical studies of medical or surgical therapy of middle ear disease are often difficult to compare, because entry criteria differ, the condition studied may not be defined clearly, definitions of success and failure differ, and follow-up intervals vary.

In planning protocols for clinical trials, investigators should consider the following factors.

1. The condition to be studied should be defined clearly.

2. If there are variables that are known or suspected to affect the outcome (age, race, sex, anatomic or environmental factors, etc), the subgroups of subjects should be identified and randomized appropriately.
3. Entry criteria and exclusion criteria should be stated clearly.
4. Definitions of success and failure should be standardized.
5. There is a place for investigating combined treatment modalities rather than only single treatment modalities.

In comparison of medical versus surgical therapy in addition to cost-benefit analysis, the psychosocial impact of surgery and the value of the prompt benefits of surgery compared with more delayed benefits of medical therapy should be weighed carefully.

Opinions have been expressed that bacteriologic cure in antimicrobial studies of acute otitis media with effusion should be documented by routine tympanocentesis on the second to fifth day of therapy regardless of clinical status. Because tympanocentesis is an invasive procedure, its justification for scientific purposes in children who are symptomatically improved needs further evaluation.

AREAS FOR FUTURE RESEARCH

1. *Deviated Septum and Septal Anomalies.* There appears to be a relation between septal abnormalities and middle ear disease. Studies should be designed to determine whether corrective surgical procedures alleviate associated otitis media with effusion. Rhinomanometric measurements may facilitate such studies.

2. *Sinus Disease.* Some reports have incriminated chronic sinus infection as a predisposing factor for middle ear disease, but well-designed studies are needed to establish or refute this relationship. If a relationship is established clearly, studies should be designed to evaluate the effects of vigorous medical and surgical (irrigation) therapy of sinusitis on otitis media with effusion.

3. *Adenoidectomy.* Recent studies have reported a favorable effect of adenoidectomy in patients with recurrent acute otitis media with effusion or chronic otitis media with effusion. However, this has been a controversial area for many years, and although the benefits of adenoidectomy in recent studies have been statistically significant, they have not been uniform. Therefore, further studies are needed to refine the data and to develop selection criteria to differentiate patients who will benefit from adenoidectomy from those who will not.

4. *Cortical Mastoidectomy.* This procedure is done on rare occasions for recurrent or refractory cases of chronic otitis media, but it is not of proven benefit. It should be evaluated critically. Because the indications are rare, a multicenter study would be necessary.

5. *Long-Stay Tympanostomy Tubes.* Long-stay tympanostomy tubes sometimes are used, particularly in children with cleft palate, but they have not been evaluated critically. Controlled studies should be done to determine whether the benefits outweigh the complications of perforation and crusting.

6. *Unilateral Chronic Otitis Media With Effusion.* Studies of surgical intervention in chronic otitis media with effusion have focused on cases of bilateral disease in which rapid improvement in hearing is a major goal. The adverse consequences of chronic unilateral otitis media with effusion need to be evaluated with regard to the need for surgical intervention and the optimal timing for intervention.

7. *Antimicrobial Therapy.* The Scandinavians use penicillin V as the drug of choice for acute otitis media, but the drug has not been compared in randomized, double-blind trials with amoxicillin or β-lactamase–resistant drugs such as cefaclor, amoxicillin-clavulanate, or erythromycin-sulfisoxazole. Such studies would be desirable. Along the same lines, the role of antibiotic-resistant bacteria in either failure of clinical response or in persistent middle ear effusion after symptomatic response has not been defined clearly. A study could be done in which patients are treated initially with penicillin V or ampicillin, and on the third to fifth day those with β-lactamase–producing bacteria would be randomized to continuing the initial drug or changing to a β-lactamase–resistant drug.

Because two controlled studies have demonstrated that 5 days of antibiotic treatment for acute otitis media is as good as 10 days, further studies are needed to determine the optimal duration of therapy (eg, 2, 5, 7, or 10 days) and whether a longer duration of antimicrobial therapy (eg, 21 days) is superior.

A search should be made for clinical criteria to identify children with mild acute otitis media who do well without antibiotic therapy.

8. *Anti-inflammatory Agents.* To date, the studies with nonsteroidal anti-inflammatory agents in chronic otitis media with effusion are not particularly encouraging, but further work needs to be done.

Conflicting results have been reported in the many studies of systemic or intranasal steroids for chronic otitis media with effusion. This question needs to be settled, and it may require a large collaborative multicenter study.

9. *Decongestants, Antihistamines, and Mucolytic Agents.* For acute or chronic otitis media with effusion, there is no apparent beneficial role for

decongestants other than symptomatic relief of stuffy nose.

The role of antihistamines or of hyposensitization in allergic children with frequently recurring acute otitis media or with chronic otitis media with effusion has not been well studied.

Animal studies and limited observations in humans suggest that the role of mucolytic agents, such as guaifenesin or bromhexine, deserves further evaluation. The mucolytic agents should be tested both in acute otitis media (given with an antibiotic) and in chronic otitis media with effusion.

10. *Environmental Factors.* In numerous epidemiologic studies of otitis media, several environmental factors have been identified as risk factors for the otitis-prone child. Manipulation of these environmental factors for prevention of middle ear disease should be evaluated in controlled studies.

MINORITY REPORT

For treatment of acute purulent otitis media with effusion, erythromycin-sulfonamide,[21,22,30] amoxicillin-clavulanate,[23,24] and trimethoprim-sulfamethoxazole[30] have been evaluated. In general, the erythromycin-sulfonamide and amoxicillin-clavulanate mixtures performed as well as amoxicillin even when on-therapy cultures were performed routinely.[30] Cefaclor was inferior[23,24,30] to amoxicillin alone or with clavulanate in three different studies when on-therapy cultures were evaluated. One of these studies showed the lack of any difference when only symptomatic improvement[23] was considered, while on-therapy cultures were showing a great difference in eradication of the infecting organisms. Trimethoprim-sulfamethoxazole was less effective than amoxicillin.[30] These studies show the clearness with which on-therapy cultures[23,30] define precisely effective antibiotics, whereas clinical outcome alone[23,28,29] may show no differences between patients, who usually are improved by the myringotomy alone.

Bacteriologic cure in antimicrobial studies of acute otitis media with effusion should be documented by routine tympanocentesis following therapy regardless of clinical status, because tympanocentesis is the only definitive differentiating procedure for partially effective antibiotics. It may be justified for scientific purposes in children who are improved symptomatically to save millions of other children from expensive and ineffective antibiotics.

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8. COMPLICATIONS AND SEQUELAE

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The Panel divided the topic of complications and sequelae into six areas that are perceived to have the most significant effects upon patients with otitis media. The areas are tympanomastoiditis, effect of otitis media on the inner ear, hearing loss, language development, vestibular function, and the effect of interventions.

TYMPANOMASTOIDITIS

RECENT DEVELOPMENTS

Uncontrolled infection results in the destruction of tissues, organs, and life itself. During the past half century the most serious sequelae of otitis media have been contained for the most part by the use of various antimicrobial agents. The potential for uncontrolled infection of the ear is still present and occurs rarely but consistently. While some of these occurrences are expected in patients with immunodeficiencies (eg, AIDS),[1] other infections occur uncontrolled for unknown reasons. Probably the most frequent type of ear infection is persistent otitis media, also called tympanomastoiditis. This may occur with or without the presence of a cholesteatoma. The infection of the mastoid bone is considered to be the same as osteomyelitis occurring in other parts of the body. There has been a study of a series of patients who have been treated with therapeutic levels of appropriate antibiotics and constant debridement of the external auditory canal.[2] The use of this noninvasive intervention may have resulted in a number of patients who have been cured of tympanomastoiditis.

Cholesteatoma can be considered as both the effect and the cause of otitis media and its more extensive manifestation, tympanomastoiditis. A possible increase has been noted in the number of cholesteatomas found in infants and toddlers with intact tympanic membranes and no history of persistent or recurrent otitis media.[3] Michaels[4] has observed an area of epidermoid cells in the epithelium of the middle ear adjacent to the ventral portion of the tympanic ring, where almost all of the primary cholesteatomas arise. It is suggested that these cholesteatomas arise from these epithelial cells. If these primary cholesteatomas are not recognized, then they will destroy the middle ear cleft and result in tympanomastoiditis.

The consequences of tympanomastoiditis still result in a number of patients who have significant conductive or mixed hearing losses. Many of these patients are not candidates for reconstructive surgery, or reconstructive surgery has not resulted in educationally or socially adequate hearing. Additionally, these patients may have continually or intermittently draining ears and/or distortions of their external auditory canal. These individuals cannot use conventional hearing aids and they may not be able to use bone conduction aids, or the bone conduction aid may not afford adequate remediation of the hearing. There are now implantable vibrators that are designed to stimulate the inner ear by bone vibration. There are two types: one is enclosed totally and driven transcutaneously,[5] and the other has a pedestal coming through the skin of the mastoid area.[6] These devices may result in better hearing for those patients for whom neither medicine nor surgery can afford educationally or socially acceptable hearing levels.

RESEARCH NEEDS

There are a number of compelling research needs in the area of complications and sequelae of tympanomastoiditis. The Panel has defined six that are substantial and can be investigated based on the present state of knowledge.

1. The first of these is the various effects of negative middle ear pressure. There is the repeated empiric observation that patients with presumed negative middle ear pressure as measured with an immittance device during determination of a tympanogram have increased thresholds for hearing. The effect of negative middle ear pressure on the sensitivity of the ear and in the areas of speech discrimination, prosody, and other dimensions should be determined. This effect may be greatest in infants, in whom there is some indication that a 10- to 20-dB increase in threshold may result in a significant degradation of discrimination.[7] Additionally, there is the question of the effect of middle ear pressure on the tympanic membrane in the formation of retraction pockets, tympanosclerosis, and cholesteatoma.

2. The inheritance of anatomic and biochemical traits that result in a heightened susceptibility to

otitis media and its sequelae now can be approached.[8] Genetically determined anatomic abnormalities that predispose to otitis media and its sequelae have been identified, eg, submucosal clefts of the palate. There appear to be other types of genetically determined anatomic variations that result in uncontrolled otitis media. These abnormalities should be identified and the genetics determined at the gene level.[9] The second area in which genetics is of importance is increased susceptibility to infection. There are numerous inherited immunologic deficiencies that have been associated with pervasive defects in the host's ability to react to an infectious agent. There is the beginning of the definition of a group of children who have a greater propensity for otitis media and its sequelae of infection. The term "otitis-prone" probably implies immunodeficiency and other host deficiencies. Many of these defects are probably of genetic origin. There is the need to define these deficiencies and to determine their genetics both from the standpoint of detection and from that of effective rational intervention at the biochemical level.

3. A third major area for research is the late fetal development of the middle ear cleft. There has been the concept that the mesenchyme of the middle ear will resorb from the middle ear cleft at different rates in different individuals. It is an open question as to whether or not this tympanic mesenchyme effects the incidence and/or the severity of otitis media in infants and the probable sequelae in older children. Another hypothesis for the cause of otitis media in infants has been formulated on the basis of repeated observation of epithelial cells believed to come from meconium and amniotic aspiration found at autopsy of the middle ear clefts of infants who have had severe perinatal problems.[10,11] Whether or not either of these two associated observations of tissue in the middle ear cleft are associated with otitis media and the sequelae, and in what ways they are associated, should be determined by both prospective clinical studies and experimental manipulation in animals.

4. Patients with both defined and undefined deficits in their microbiologic defense systems appear to be affected most severely by the sequelae of the infectious processes of otitis media. These deficits involve the entire defense system, which includes the T cells, B cells, phagocytosis, cell repair, cell regeneration, and cell renewal. Many of these defects are probably genetic, and some are acquired, as in AIDS or immunosuppression secondary to the use of various medications. There are undoubtedly a number of these defects that are primarily genetic but are latent until induced by environmental stimuli. These conditions most probably may be found in "otitis-prone" patients. This group should be studied carefully for the determination of defense mechanism abnormalities so that they can be identified and cared for in a rational fashion, instead of the presently used empiric approach.

The determination of who is "otitis-prone" is now made (with the exception of a known entity such as cleft palate, Kartagener's syndrome, or DiGeorge syndrome) only after the child has had a large number of infections and has been a victim of sequelae. Certainly the world scientific community should be able to develop a method to predict otitis media and prevent it and its sequelae from occurring. The investigation of the deficits in defense mechanisms, both acquired and genetic, is one of the most significant and compelling research needs. It is felt that there should be a significant allocation of resources, both in personnel and in wealth, over the next half decade in the area of susceptibility to disease.

5. One of the more common sequelae of otitis media is the effect upon the tympanic membrane and the middle ear cavity. There are various changes that are observed and are categorized diffusely as "scarring," "tympanosclerosis," "monomembrane," "atrophy," "retraction," etc. Very little information is available concerning the cellular renewal of the tympanic membrane. There is a need for identification of the types of abnormalities that otitis media will induce in the tympanic membrane. Following this, there is a need to know the natural history of these changes in the tympanic membrane. Will the "tympanosclerosis" remain for 1, 5, 10, or more years? Will a retraction pocket always, often, sometimes, occasionally, or never become a cholesteatoma? These and many other questions have not been answered. The answer lies in understanding the normal cell biology of the tympanic membrane, not only that of cell renewal, but also that of the cellular processes that occur.[12] The same concepts for the types of injury and repair should be directed also toward the middle ear and its mucosal lining.[13]

6. The last critical area of study of complications of otitis media as a cause of tympanomastoiditis is the evaluation of surgical interventions that now are being carried out. There are a number of standard operative procedures that have been used for the past three quarters of a century to care for the sequelae of otitis media. All of these fundamental procedures were developed in the preantibiotic era, with some modification, especially in the domain of tympanoplasty, occurring during the early part of the antibiotic era. There has been no systematic, rational, prospective study concerning the appropriateness or efficacy of these procedures. This is especially important if one considers that the probable nature of our care of these diseases has changed radically since the operative procedures were designed. One of the reasons for this probably lies in the heterogeneity of diseases and the great differences in operative techniques. The stochastic inferences of multiple dimensions now can be carried out with a desktop computer. All that is needed is

the proper questions and the objective prospective compilation of data. The next half decade should be characterized by the lessening of 19th-century pragmatic surgical empiricism and the advent of rationally designed and evaluated interventions.

EFFECT OF MIDDLE EAR INFECTION ON INNER EAR

RECENT DEVELOPMENTS

Sensorineural hearing loss has been described clinically as following chronic middle ear disease. It can be either a natural development of otitis media or the result of usage of topical otic antimicrobial preparations. Additional evidence has been presented to support the hypothesis that both acute purulent otitis media and chronic otitis media can cause high frequency sensorineural hearing loss in humans.[14] In the chinchilla model of pneumococcal otitis media, significant sensorineural hearing loss at high frequencies is demonstrated.[15] These findings influence clinical considerations for treatment of middle ear infection.

Numerous studies in animal experiments have proven the ototoxicity of antiseptics used as a preoperative sterilizing agent and the ototoxicity of antimicrobials currently being used for treatment of ear disease.[16-20] High performance liquid chromatography has made it possible to quantify the concentration of neomycin in the perilymph.[21] After direct and continuous application on the round window membrane, the drug quickly penetrated the perilymph. Although considerable variations exist, cochlear damage studies by light microscopy indicate that damage increased as neomycin application time became longer. Detailed distribution of horseradish peroxidase in the inner ear after injection into the middle ear cavity also is reported by Saijo and Kimura.[22]

There is a lack of concordance between human and animal studies. These contradictory findings between clinical experience and experimental results may be due to several factors that can be classified broadly as structural and procedural. The structural factors include anatomic differences between humans and experimental animals. The most common laboratory animals used for ototoxicity studies are the guinea pig and the chinchilla. Both species have a round window that is expressed openly in the middle ear cavity, unlike the human round window, which is recessed deeply in a narrow niche. Perhaps more important is the difference in thickness between the rodent and human round window membrane. The human membrane is thicker and has a greater collagen density than the rodent membrane. Nomura et al[23] documented that a pseudomembrane often drapes the human round window. These factors could afford a greater barrier to the passive diffusion of a drug from middle to inner ear.

Higher frequencies are the first to be affected by toxic agents present in the middle ear. Common audiologic practice ignores testing above 8 kHz because of the imprecision of calibration at the higher frequencies and the greater importance of the "speech frequencies" to humans. Thus the procedures used in the assessment of hearing loss often ignore those frequencies most likely to be affected by topical agents.

Autoimmune disease as it relates to sequelae of otitis media is another important area to be studied. Recent clinical reports offer ample evidence that systemic immunologic disturbance is the cause of sensorineural hearing loss.[24-29] Arnold et al[30] and others[31,32] demonstrated that antibodies are directed specifically at the epithelial cells and the mesenchymal structure of the inner ear tissue. Recent animal studies by Harris and Ryan[33] reported strong immune responses to local antigen challenge in the middle ear of animals sensitized to keyhole limpet hemocyanin. Yoo et al[34] reported that the rat model of type II collagen-induced autoimmune ear disease developed sensorineural hearing loss. To date, however, hard evidence of an immune disease as a result of otitis media or a mechanism of development of sensorineural hearing loss in otitis media is lacking.

RESEARCH NEEDS

1. *Effect of Middle Ear Infections on Inner Ear.* Studies of the effect of middle ear cavity inflammation per se on inner ear function are lacking. Alterations of round window membrane permeability with the presence of middle ear inflammation must be studied. Treatment of otitis media with otic solutions is common because of its convenience and therapeutic usefulness. Otic preparations are meant to treat infection and accompanying inflammation in the middle ear cavity, but some of them may elicit unspecific inflammation due to the nature of the chemical or due to unbalanced pH and osmolarity.

Advantages and disadvantages of using otic drugs should be discussed with a clear understanding of the effect of middle ear infection in the inner ear.

2. *Ototoxicity of Otic Antimicrobials.* There are differences in vulnerability to topical otic preparations in humans and rodents, and a potential for ototoxicity from these preparations exists in clinical use. The need for experimental examinations of topical ototoxicity still exists, but the emphasis should be placed on scaling animal studies to humans and in recommending the least toxic substances with equivalent clinical efficacy. Otic preparations' relative ototoxic potential in humans can be inferred experimentally by employing the standard pharmacologic paradigm of dose-response curves in different species of animals with different anatomic structures of the round window membrane.

3. *Definitions of Protective Barriers.* Protective barriers can be immunologic and anatomic and may be determined genetically. The differences in the barriers among humans and other species need to be studied.

The Panel feels that autoimmune disease in otitis media and its relationship to sensorineural hearing loss is an important issue and needs further study.

HEARING LOSS

RECENT DEVELOPMENTS

Since the last Symposium, advances have been made in obtaining definitive tests in young infants with otitis media. Auditory brain stem response audiometry has been reported on such infants, showing that the degree of hearing loss in children under 12 months of age when otitis media is present resembles that of older children with otitis media who can be tested conventionally.[35-37] In addition, visual response audiometry has permitted more rapid evaluations of the young infant and is in common use.

One of the most dramatic findings recently reported is the heretofore unknown educational impact of monaural hearing loss on the child. A classic study by Bess[38] has shown that not only do children with monaural losses repeat school years significantly more than those who hear from both ears and need resource help more than normal-hearing children, but children with right ear deafness have five times more chance of failing 1 year or more than do normal children. This finding raises a question of right ear dominance, and although the study involved children with severe sensorineural deafness, there may be some extrapolation to the mild conductive loss accompanying otitis media.

Speech science has provided some provocative ideas in relation to otitis media. Eimas and Clarkson,[39] who compared otitis-prone children with a non–otitis-prone group in their investigation of discrimination of voice onset time, concluded that early recurrent otitis media can produce subtle deficits in the abilities of children to categorize the sounds of speech and to use lexical status to derive this representation. They also speculate that an independent genetic predisposition for speech and language delays exists that may compound the effect of otitis media out of proportion to the sum of the two contributions. Their studies open the way to relating specific auditory learning functions to degrees of hearing loss.

Nozza[37] has suggested that the young infant has poorer auditory thresholds than the older child, and that the addition of a mild hearing loss from otitis media greatly increases the handicap of auditory processing. His findings point to the paucity of information on what is heard with various degrees of a conductive loss and its effect at different ages.

The effect of early otitis media history on super-high frequencies has been suggested in one study[40] showing that by the third grade, children with a history of otitis media show a significant reduction in their hearing at 18 kHz.

RESEARCH NEEDS

The developments cited above strongly indicate the need for further research to study the relationship between the hearing loss of otitis media and other sequelae of otitis media. The questions to be answered include

1. Can further auditory brain stem response studies be used to determine the normal auditory abilities in infants of different ages, both normal and otitis prone? What other ways can this be measured?

2. Can speech science give us more information on what is being heard by the child with various degrees of hearing loss from otitis media? What specific auditory learning functions are affected, and in what way, by different degrees and types of loss?

3. Does unilateral otitis media affect the language learning of children, as suggested by the Bess[38] study?

4. Is right ear dominance a factor in producing more language sequelae from otitis media? What is the effect of unilateral right ear otitis media as compared with left ear otitis media?

5. What is the natural history of super-high frequency hearing in otitis-prone children? Does any permanent sensorineural hearing loss result from early recurrent otitis?

6. What is the relationship of otitis media conductive hearing loss to a) parent-child bonding, b) vocabulary deficits, c) language learning deficits, d) aberrant behavioral patterns, and e) reduced educational achievement?

LANGUAGE DEVELOPMENT

RECENT DEVELOPMENTS

Prospective and Longitudinal Data Showing Positive Correlation. Frequently, criticism of previous research into the possible sequelae of speech-language deficits has centered on the lack of prospective, longitudinal data. Within the last 5 years, however, several investigations have sought to correct this problem in their research design.

1. The Boston Collaborative[41] has been prospectively following a large group of children from various socioeconomic groups since birth. Medical, otologic, communicative, developmental, and academic outcome data are now becoming available on

these children. For example, Teele et al[41] reported that at 3 years of age, children from middle-income families with early histories of persistent otitis media demonstrated significantly poorer performance on tests of lexical competency (Peabody Picture Vocabulary Test), auditory comprehension, and verbal abilities (Preschool Language Scale) than children from the same socioeconomic background without significant early otitis media histories.

Recently, Menyuk,[42] of the same collaborative study, found that by 7 years of age, children with histories of recurrent otitis media (otitis positive) during the first 3 years of life had reduced expressive lexicons and poorer morpheme production than their peers with low-incidence otitis media histories (otitis free). Perception of morphologic information was not affected. Otitis-positive children also performed less well in the production of complex sentences, while receptive sentence comprehension was unaffected. Both speech sound (phonologic) production and perception were influenced negatively by early, recurrent otitis media. Thus Menyuk concluded that the effects of otitis media are observable in the speech and language abilities of school-age children. Further, he observed that as a group, children with speech and language deficits did not "catch up" with their otitis-free counterparts. As noted previously, the effects on language appeared to be predominantly expressive rather than receptive in nature, except in the case of phonologic perception.

Finally, Klein et al[43] (from the Boston group) also reported that 7-year-olds with persistent effusion during the first 3 years of life had poorer cognitive abilities (performance and verbal IQs) as measured on the revised Wechsler Intelligence Scale for Children. The group had lower scores on standardized academic achievement tests than 7-year-olds considered otitis free through age 3 years. Increased time spent with otitis media was related to lower achievement in mathematics and a tendency toward poorer reading ability.

2. Friel-Patti et al[44] reported on infants (predominantly premature) from low socioeconomic backgrounds. All babies were followed longitudinally through 24 months of age. Pneumatic otoscopy and tympanometry were used to detect otitis media, and the auditory brain stem response documented auditory sensitivity. Friel-Patti et al found a significant effect of otitis media on language development as measured by the Receptive Expressive Emerging Language Scale and the Sequenced Inventory of Communication Development. They also found a relationship between reduced auditory sensitivity as measured on the auditory brain stem response and the severity of language delay. A more detailed prospective investigation was started in December 1984 involving children from middle-class backgrounds.[45]

3. Wallace et al[46] investigated the emerging language abilities of infants at 1 year of age who had been followed for otitis media beginning at term or 40 weeks' conceptional age. A group of high-risk infants (predominantly of very low birth weights) and full-term control infants were followed prospectively. All infants were of low socioeconomic status. Pneumatic otoscopy was used to document infants who had otitis media bilaterally at 30% or more of their first-year medical visits, and were considered otitis positive for the purposes of the study. Regardless of birth status, otitis-positive infants demonstrated significantly lower expressive language abilities as measured on the Sequenced Inventory of Communication Development than infants considered to be otitis free (normal otoscopic results bilaterally at >80% of first-year visits). The groups did not differ with respect to receptive language or cognitive status. As a group, infants considered otitis positive had poorer auditory sensitivity than otitis-free infants as assessed by frequent auditory brain stem response evaluations completed during the first year.[47,48]

4. Downs et al[49] completed a 4-year prospective study of preschool children who were followed through a regular pediatric practice. All children received a language screening test (Early Language Milestone Scale). The authors found that increased episodes of otitis media in early life tended to be associated with increased failures on the expressive section of the test.

Studies Showing Negative Correlation. In contrast to these findings, which suggest a negative influence of early, persistent otitis media on speech and language capabilities, several investigations over the past 5 years have found no relationship between otitis media and later speech-language outcome.

1. Roberts et al[50,51] reported no relationship between increased days with otitis media and speech and language abilities. In their study, the course of otitis media was well documented on a near-daily basis as part of a comprehensive intervention program instituted at birth. All children were of low socioeconomic status. The children received an enriched preschool program: 5 days per week, 50 weeks per year. No significant difference in language outcome was seen between children with high numbers of days with otitis media versus those with low numbers of days with otitis media during the first 3 years of life. These investigators reported no association between early otitis media and later language outcome.

2. Lous et al[52] reported on a study of 8-year-old Danish children who were followed beginning at 3 years of age. A group of subjects who had otitis

media or type C tympanograms four times within a 6-month period at age 3 were compared to matched control children who had normal middle ear function for the same period. At age 8, performance between groups was no different for tests of vocabulary, intelligence, or reading achievement.

3. In a case-control study, Hubbard et al[53] studied two groups of cleft palate children. One group received early and aggressive surgical intervention (myringotomies with tubes) as a prophylactic for otitis media. The other group received more conservative otologic management. The subjects did not differ on any demographic or craniofacial characteristic. Hubbard et al[53] reported that the two groups differed in hearing level on the day of assessment and in percentage of articulation errors as measured on a standard clinical articulation test (Templin-Darley). No difference between the two groups was reported on measures of social, cognitive, emotional, or language development. The sole language measure used was the verbal subtest of the Revised Wechsler Intelligence Scale for Children.

Other Nonprospective Studies. Other nonprospective studies have found that otitis media negatively influences speech and language competency. Unfortunately, the lack of specific documentation of these studies' early otitis media histories makes the interpretation of results more difficult.

1. In a prospective study in the Netherlands of children 2 through 4 years of age, Rach et al[54] found that children with persistent otitis media from 2 years of age had poorer expressive language abilities than those considered otitis free for the same period. Receptive abilities were no different between groups.

2. Shriberg and Smith[55] reported on the phonologic capabilities of children identified with speech production deficits of unknown origin. The children were separated into two groups based on a positive or negative early history of otitis media. The phonologic errors of the otitis-positive group differed from those made by the otitis-free subjects. Errors were classified into two sound-change categories. The proportion of speech-sound errors made by the otitis-positive children was significantly greater than that of the otitis-free children for both sound-change groups. These errors included substitutions and omissions of initial consonants and nasal substitutions, distortions, and stop-consonant replacements. While no specific patterns of speech-sound errors were displayed consistently by children with early histories of otitis media, as a group their errors differed from those displayed by otitis-free children.

3. Eimas and Clarkson[39] used traditional adult speech discrimination and identification paradigms with children to examine speech processing at a phonetic level. They studied two groups of children who ranged from 5 to 6 years of age. The group considered to have positive early otitis media histories categorized (identified) speech sounds less consistently than the otitis-free group. Otitis-free children demonstrated clearer differentiation of the end point stimuli on a 12-step voice onset time continuum than the otitis-positive group. Further, the voice onset time value of the boundary (changeover) stimulus was longer for the otitis-positive than the otitis-free subjects. Discrimination of speech sounds (a "same-different" task) was also markedly different between the two groups. Overall, the otitis-positive group performed more poorly than the otitis-free children; the former group showed no clear phonetic boundary effect. In an additional experiment, otitis-free children were better able to use "supplemental" lexical information during an identification task than otitis-positive subjects.

4. Feagans[56] has contributed to our understanding of the possible behavioral repercussions of early otitis media, and the implications of those behavioral problems for remediation programs. Specifically, Feagans has proposed a model of how fluctuant hearing loss associated with persistent otitis media may relate to later attentional deficits and poorer performance in the academic environment. Feagans demonstrated that while no specific language deficits were present in otitis-positive children at school age, children within this group had significantly more difficulty attending to tasks in the educational environment.

RESEARCH NEEDS

Continuing controversy exists regarding the effects of persistent otitis media on speech-language acquisition and competency. Moreover, debate continues over the issues of long-term outcome and/or the reversibility of communication delays or deficits. While recent studies have more carefully controlled research design, dichotomous conclusions regarding language and otitis media still persist. Several issues remain unresolved.

1. The existence of a "critical" or, more accurately, a "sensitive" period for language acquisition is in question. That is, are there particular ages that are crucial to normal speech and language acquisition such that a mild, fluctuating hearing loss could adversely affect emerging oral communication? Further, is the impact of otitis media related to the degree, type, and/or duration of episodes? Menyuk[42] suggests that the first 3 years of life are crucial in the development of normal communicative competency. Does otitis media after that age have no effect on speech and language development?

2. At very young ages, the acoustic properties of speech provide the basis for emerging phonology

and syntactic structures.[42] Does transient mild conductive hearing loss affect the perception of individual speech phonemes, thereby delaying the acquisition of normal phonology and syntax? Can specific deficits in receptive and expressive communication skills be identified prior to the complete emergence of speech and language?

3. Is infant audition more affected by conductive hearing loss than the audition of older children and adults? That is, are behavioral "thresholds" for speech reduced to a greater degree than would be expected for a "mild" loss of hearing[7,37]?

4. Determinations of language-risk states may vary among groups of infants and young children depending upon multiple nonmedical variables. Such factors may include socioeconomic status, living environment, family size, communicative style of the caregiver, and genetic predispositions for language problems (eg, developmental language delay, dyslexia). Recent evidence suggests that the effect of otitis media may be synergistic for certain groups of children, while others apparently are not influenced by its course. Secondary factors that are either positive or negative in their effect on certain groups of children with otitis media must be identified. As an example, the recent report of Roberts et al[51] found no relationship between otitis media and language outcome for children of low socioeconomic status. However, the intervention program may actually have exerted a positive effect on children who experienced repeated episodes of otitis media. We are in need of controlled studies that examine these nonotologic variables.

5. Assessments of the communicative competency of school-age children must include a battery of test instruments that are sensitive to subtle nuances of emerging receptive and expressive language. Generalizations on the effects of otitis media often are made on the basis of only one specific test[53] rather than on a battery of measures. Each area of receptive and expressive language competency (phonologic, syntactic, semantic, and pragmatic) must be assessed thoroughly for researchers to understand fully the influence of otitis media on communication development. Such standardized measures are not presently available for infants and young children.

6. Prospective studies of the effects of early otitis media on academic performance have been done only recently.[43] Additional outcome studies are necessary to replicate or refute such findings. In particular, we need to understand the relationship of early otitis media to reading and mathematics skills. Behavioral problems and their relationship to otitis media[56] is an area in need of further research.

7. Of specific interest to the understanding of otitis media and language development may be the study of auditory evoked potentials, specifically the late cortical and cognitive evoked potentials. These electrophysiologic indices may provide insight into the brain's capacity to process speech and language information, thereby providing another means to examine infants and young children at risk for communication deficits.

8. Finally, we must embark upon the study of effective remediation strategies for children identified as having delays in emerging language. These strategies should include the development of team intervention programs that are supported by medical, communication, and developmental specialists.

CHANGES IN VESTIBULAR FUNCTION AFTER VARIATIONS IN MIDDLE EAR PRESSURE

RECENT DEVELOPMENTS

The middle ear and inner ear both constitute different compartments in the ear. Although these two entities have been dealt with separately in both experimental and clinical research, they are closely interrelated within the ear. Influences from the middle ear may readily affect the inner ear via several routes such as the oval window and the stapes footplate, the round window membrane, blood and lymph vessels, or even bone lacunae. Thus pressure changes, chemical substances, temperature changes, etc, are transmitted easily from the middle ear to the inner ear. It is established that inflammatory conditions in the middle ear (especially infection) may affect the inner ear with ensuing high frequency sensorineural hearing loss. This cochlear change is thought to be brought about by invasion of toxic substances, possibly through the round window membrane into the basal coil of the cochlea.

External pressure changes as well as pressure changes confined to the middle ear have been shown to affect the inner ear; thus vestibular dysfunction has been described in connection with pressure changes during diving or flying.[57,58] Vertigo and threshold shifts in hearing have been reported after exposure to infrasound.[59,60] The possibility of eliciting vertigo by applying local overpressure in the middle ear was demonstrated by Ingelstedt et al.[61] The connection between inner ear symptoms and ambient pressure changes was first shown in patients with Meniere's disease by use of a pressure chamber.[62,63] The inner ear pressure-regulating mechanisms were investigated in animal experiments by Densert et al.[64]

Densert et al[65] showed in cats that experimentally induced changes in the middle ear pressure (positive as well as negative) were followed immediately by almost equal positive and negative pressure changes within the perilymphatic compartment. When the cochlear aqueduct was blocked, the perilymphatic pressure response consisted almost exclusively of the first phase of the response, while the rebound phase disappeared almost completely. On the basis of these findings, patients with clinically manifested Meniere's syndrome were subjected to changes within a pressure chamber. The results of this investigation support the hypothesis that the use of overpressure creates changes in the hydrodynamic properties of the cochlea that are reflected in an improvement of the inner ear frequency analysis.

The effect of middle ear effusion on the vestibular system was shown by Honjo et al.[66] By use of a posture platform it was shown that patients with bilateral middle ear effusion had a righting reflex that made them prone to increase the tonus in their neck muscles. The head was rotated to one side thus slightly, indicating an imbalance in the postural system. This was interpreted as being caused by an influence on the vestibular receptor on the affected side.

RESEARCH NEEDS

The next issue to be illuminated in this field is the direct connection between the middle ear and the inner ear. Thus, it is of great interest to investigate possible mechanisms for the above-mentioned influence. It may be mediated by separate mechanisms of interaction between the middle ear and the inner ear. Studies of these interaction mechanisms should include properties of permeability between the middle ear and the inner ear. The passage rate of toxic substances possibly exerted by middle ear condition also should be included in such studies. It is conceivable that toxic products may be developed during the period of secretory otitis media, affecting the inner ear. The interaction between the middle ear and inner ear pressure conditions is also important to investigate by several different approaches.

In the clinical situation, patients with unilateral or bilateral secretory otitis media, with or without vestibular symptoms, should be tested with sophisticated methods analogous to those presented by Honjo et al.[66]

INTERVENTION

RESEARCH DEVELOPMENTS

The complications of sequelae of otitis media have resulted in a number of advances in care. These include a) implantable hearing aids, b) antibiotic therapy, and c) educational habilitational intervention that has been discussed in this and other sections of the Panel Reports.

The Panel has addressed the need to assess these interventions as to their efficacy and efficiency. The three major forms of intervention — medical, surgical, and educational — all need to be evaluated in a prospective fashion to determine if they really ameliorate the effect of otitis media. Their efficiency in terms of cost benefit also must be assessed. This should be a major effort for the next decade.

RESEARCH NEEDS

There are at least two special areas that need to be identified by the Panel, concerning the more common surgical interventions. There has been evidence that adenoidectomy is useful in some children[67] in reducing the number of episodes and consequently the sequelae of otitis media. It is not known why adenoidectomy has been effective. There should be investigations directed at the understanding of the anatomic and cellular mechanisms that result in this effect. This will allow for selectivity in the choice of intervention and probably will allow for the design to be more effective and perhaps less invasive and intervention less costly.

The second area concerns the widespread use of the tympanostomy tube. Tympanostomy tubes are associated with various complications including otorrhea, persistent tympanic membrane perforations, etc, but despite their deficiencies they are commonly used and may represent a better means of caring for some patients with otitis media. They also may prevent some of the sequelae. There is a need for research to determine why these prostheses work when they do, how to maintain them until they are not needed, how to improve the hearing results, and how to decrease the infection and other sequelae associated with their use. Study of tympanostomy tubes should be a major research effort for the next decade.

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EFFECTS OF BLAST OVERPRESSURE ON THE EAR

Editors
COL JOAN T. ZAJTCHUK, MC, USA
LTC YANCY Y. PHILLIPS, MC, USA

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BLAST INJURIES OF THE EAR IN MILITARY OPERATIONS

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COL JOAN T. ZAJTCHUK, MC, USA

WASHINGTON, DC

Exposure to blast waves from the explosion of ordnance is a common feature of combat operations. The ear is the organ most sensitive to such strong pressure waves. Blast damage to the ear may range from minor acoustic trauma to major disruption of middle and inner ear structures. Standard hearing protectors should offer a significant degree of shielding from these injuries. Aural injury alone seldom should cause a soldier to abandon a combat mission. However, the potential for a large temporary or permanent neurosensory hearing loss does raise issues about such a soldier's effectiveness on the modern, communication-intensive battlefield. Further research is necessary on mechanisms of injury, protective measures, and the effect of hearing loss on military performance.

KEY WORDS — blast injury, ear, hearing, military medicine.

Explosions are inherent in modern warfare, and while they may injure solely as a result of impingement of the resulting blast wave on a victim, injuries from fragments and thermal effects have caused far more casualties in wartime. Because of changes in the types of munitions that might be employed in future wars, and as a direct result of more efficient defensive systems for the soldier, the US Army has looked more closely at the threat of direct blast injury in modern combat operations. Considerable interest has focused on the danger of blast waves in confined spaces in which such percussive effects may be the most serious casualty risk. All gas-containing structures of the body are susceptible, but because of its physiologic function as a transducer for even weak pressure waves in air, the ear is particularly sensitive to blast waves.

In an effort to better understand the risks and consequences of blast injury to the ear, the Office of the Surgeon General of the Army and the US Army Medical Research and Development Command sponsored a seminar at the Walter Reed Army Institute of Research on Sept 26 and 27, 1986. The meeting was attended by invited guests from the civilian community and the other armed forces. The papers contained in this symposium were presented and discussed at some length in an open forum. This paper represents the authors' summary of those deliberations as they relate to immediate questions facing the Army. The opinions expressed herein are not necessarily those of the Department of the Army or the Department of Defense. The interested reader is referred to the individual papers and their references for further details.

Injury to the ear is a common consequence of exposure to a blast wave. Such injury may be particularly frequent inside rigid structures in which the blast may be contained and reverberate off the walls. This is likely inside an armored vehicle penetrated by a shaped-charge antitank munition or inside reinforced buildings. The resultant aural injury may range from a trivial insult to a major disruption of middle and inner ear structures. Hearing loss with or without eardrum rupture will occur most frequently with persistent pain, distracting tinnitus, or vestibular dysfunction being much less common. With the stress of combat and the shock of a proximate explosion, the soldier may be initially unaware of the aural injury. In a combat setting, soldiers having only aural injuries without vestibular disturbance would have a low priority for medical evaluation and evacuation. Although morale and the motivation to fight are difficult to quantitate, with few exceptions such soldiers would be expected to complete a combat mission.

By itself, a tympanic membrane ruptured by a pressure wave is not likely to be the cause of significant acute disability. Fewer than 5% of such ruptures should be associated with incapacitating pain or balance disturbance. Barring infection, the vast majority will heal without intervention. Some 10% to 20% ultimately will require surgical closure, and a small percentage of patients can expect chronic problems from infection or cholesteatoma.

The presence of a ruptured tympanic membrane is an indication that some damage is likely in the cochlea. Following such a blast, a soldier may be rendered functionally deaf for a period of minutes and is likely to have a measurable loss for hours, if not permanently. The hearing can be expected to recover most rapidly and completely if the individual is afforded noise avoidance by the continuous use of a good hearing protector and/or by being assigned to quiet duty. The latter is likely to be a rare commodity in active combat. The possible performance decrement associated with a significant hearing loss cannot be evaluated at present. Modern

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REPRINTS — LTC Yancy Y. Phillips, MC, USA, Dept of Respiratory Research, Walter Reed Army Institute of Research, Washington, DC 20307-5001.

combat operations are a communication-rich environment in which the soldier must acquire and process a great deal of aural information and act upon it quickly and decisively. Effective listening is made more difficult in military operations by the high background noise level, the complicated information content of messages, and the problems of multilingual communication. A hearing-impaired soldier on guard duty or one assigned radio communication responsibilities may be more of a liability than an asset.

The aural effects of blast are lessened greatly if effective hearing protectors are being worn at the time of exposure. This is likely to be true of both insertional and circumaural devices. Hearing protectors cannot be worn during all combat operations. However, if the tactical situation permits, hearing protection can guard against both blast injury and the more common noise-induced hearing loss associated with the impulse noise of weapon firing and the high intensity continuous noise of engines, armored vehicle tracks, and helicopter blades. Passengers inside armored personnel carriers being conveyed into battle are ideal candidates for such hearing protectors, which then can be discarded readily when dismounting for combat.

Further research is necessary in order to better define the problem of aural blast injury, to assure its prevention, and to define its performance consequences. The entire range of structural and functional disturbances of the inner ear must be addressed. The shielding effects of standard-issue hearing protectors must be validated in strong blast fields. Perhaps most important, the effect of hearing loss on the performance of military duties must be evaluated carefully. Demonstrating a loss in combat effectiveness due to hearing loss, if one indeed does exist, will help commanders see the value of enforcing the use of hearing protection in both combat and training.

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OTOLARYNGIC HEALTH SERVICE SUPPORT IN THE AIRLAND BATTLE

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WASHINGTON, DC

The Blast Injuries of the Ear Seminar was conducted to better define the state of knowledge about the medical care and consequences of blast injuries of the ear in battle. The immediate concern of this discussion was the relative importance of the finding of widespread eardrum ruptures in penetrating attacks by shaped charge munitions against the Bradley Fighting Vehicle and the M113 Armored Personnel Carrier. In order to focus on the care of the soldier with such injuries, a brief description of the current medical care and evacuation chain of the US Army, as well as the proposed future evacuation chain in the Airland Battle scenario, will be discussed. Detailed treatment of patients will be discussed in the descriptions from the Quad Service Clinical Data Base regarding wounds of the tympanic membrane. Most blast injuries of the ear would not be considered as incapacitating casualties by the Army Medical Department, except in severe circumstances.

KEY WORDS — blast injury, ear, hearing.

In past conflicts, the expected distribution of 10,000 hits, by regional location and type of casualty resulting, revealed the following information.[1] Of approximately 2,000 soldiers with wounds of the head, neck, and face, 1,000 were living, with the remaining dead of wounds or killed in action. The probability of occurrence of perforated, lacerated tympanic membrane wounds amounts to an incidence of approximately 0.0028 of all combat-inflicted wounds. In the following discussion, only otolaryngic care and treatment of these wounds will be discussed.

In the US Army System of Casualty Handling the combat zone (CZ) hospitals are at the corps level (Fig 1). It is only at the evacuation (EVAC) hospital that otolaryngologists first provide their services. In this hospital the use of the operating microscope as well as the ancillary support services of neurosurgery, oral surgery, and ophthalmology are provided. In past conflicts, in the CZ, patients could arrive in any routing sequence from the battalion aid station, the clearing station, the mobile army surgical hospital (MASH), or the combat support hospital (CSH) to the final destination for otolaryngic evaluation at the EVAC hospital, the field, or the general hospital. Because past American air superiority allowed for virtually unlimited air evacuation, wounded soldiers often were removed from the battlefield within 30 minutes to be treated by the appropriate specialist.

In the projected conflicts of the future, it is expected that lines of communications may be closed, without air superiority, so deep operations would be necessary. Extended distances for air evacuation would require enhanced forward medical care with increased patient-holding capabilities. There would be increased reliability on logistical support as well as the use of modular medical support elements to provide these medical treatment facilities with augmented surgical care and holding units. Greater mobility for these modular units in the forward areas of battle as well as the increased number of holding beds would insure a greater number of return to duty (RTD) patients, rather than evacuating those less seriously injured to a higher echelon of care and thereby losing them to the battle. Limitations of this system require the reorganization of Army Medical Department resources both in personnel and equipment, and an increase in the number of fixed beds in the United States. These beds would be in military hospitals, in the Veterans Administration and in nonfederal hospitals. The operational concepts for Health Service Support demand an optimization for transportation of the sick and wounded and because RTD soldiers are expected to be the principal source of personnel reinforcements in this type of battlefield scenario. The Airland Battle applications will be functional through the year 2000. In order to clarify the difference in evacuation routes for the current as well as the future system, a detailed description of the current medical system will be given.

CURRENT MEDICAL SYSTEMS CONCEPT OF OPERATIONS

Under the current policies,[1,2] sick or wounded soldiers in the CZ who are unable to return to duty within 7 to 15 days are evacuated to a higher level of care. The MASH, the CSH, and the EVAC hospital all have intensive care units to treat the seri-

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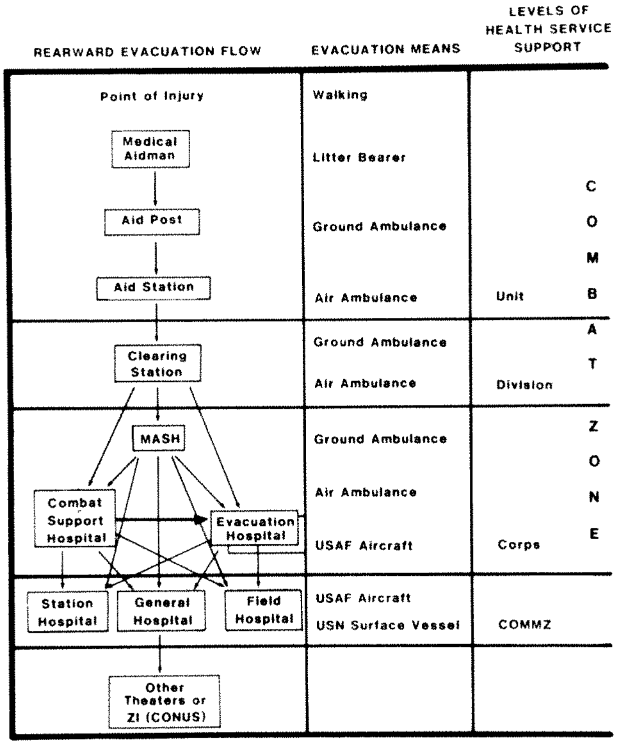

US ARMY MEDICAL DEPARTMENT NORMAL EVACUATION CHAIN

Fig 1. US Army System of Casualty Handling. Present system of rearward evacuation of sick and wounded shows means of transportation to higher level of health care support in theater of operations. Each higher level has more sophisticated medical and surgical care. Combat zone (CZ) hospitals are mobile Army surgical hospital (MASH), combat support hospital, and evacuation hospital. Clearing stations provide emergency care. ZI — zone of interior, CONUS — continental United States, USAF — US Air Force, USN — US Navy, COMMZ — communications zone.

ously injured. The CSH and EVAC hospitals also have intermediate-care and minimal-care wards. Under this current evacuation policy, very little emphasis is placed upon returning a patient to duty after minor injuries or illnesses. Limited bed holding capacities at these forward hospitals demand a continual evacuation of patients to other, larger facilities.

Mobile Army Surgical Hospital. This hospital cares for up to 60 patients in the preoperative area or the intensive care ward. It provides for resuscitative surgery and medical treatment to prepare the critically injured or wounded for further evacuation and provides emergency surgery to save life and limb. It is generally located in the division rear area according to the tactical situation, is considered to be 100% mobile on one airlift, and theoretically can be reestablished within 7 hours.

Combat Support Hospital. This hospital provides for up to 200 patients and includes all the services of a MASH unit in addition to inpatient oral surgery and dental services. It is approximately 35% to 50% mobile, requires two or three airlifts for movement, and generally provides less urgent surgical care. Reestablishment of this hospital after a move requires 24 to 36 hours.

Evacuation Hospital. Hospitalization for up to 400 patients is provided as well as resuscitative and definitive medical and surgical care preparing patients for RTD or further evacuation. It is considered to be 10% to 25% mobile and has the services of otolaryngology, neurosurgery, ophthalmology, urology, oral surgery, thoracic surgery, maxillofacial surgery, and psychiatry. Additional medical or surgical teams and supporting equipment are added as needed. Direct admissions come from the unit or from the CSH or MASH.

In the current evacuation system in the CZ, head and neck trauma treatment is provided by oral surgery and general surgery at both the MASH and the CSH. Otolaryngology specialty care is added at the EVAC hospital level and above. Additional surgical service teams and equipment can provide increased staffing personnel in general surgery, orthopedics, shock/intensive care, maxillofacial surgery, neurosurgery, thoracic surgery, anesthesiology, ophthalmology, and otolaryngology. These teams are 100% mobile and provide both officer and enlisted medical personnel and equipment for inpatient and outpatient care. These teams can be added to any hospital in the CZ or communications zone (COMMZ).

The COMMZ hospitals have an evacuation policy of 30 to 60 days, provide more sophisticated medical and surgical care, and prepare patients for further evacuation to the continental United States (CONUS).

AIRLAND BATTLE

In the airland battle of the future,[3,4] the evacuation of patients to more specialized hospitals is done early in the triage chain at a division level health care facility. The goal is to separate those RTD patients requiring minimal care from those patients who would need medical evacuation to more sophisticated hospitals in the CZ, to a general hospital in the COMMZ, or to CONUS (Fig 2). This medical regulating system places emphasis on far-forward trauma triage and treatment as well as prevention of medical diseases. Casualties are directed to three theater hospitals in the corps region: the CSH, the EVAC hospital, and the general hospital.

The CSH would treat primarily RTD patients. The EVAC hospital specializes in trauma care, with some patients returning to duty if care and convalescence falls within the 30-day evacuation policy. Further evacuation to a general hospital provides follow-up, treatment, and stabilization prior to patient movement to CONUS or to a convalescent area prior to RTD (area support medical

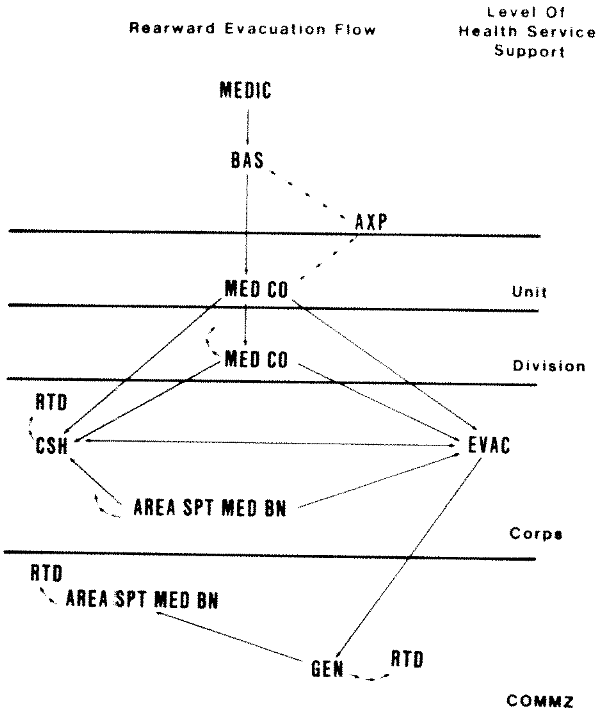

Fig 2. US Army Airland Battle Doctrine System of Casualty Handling. Proposed system of rearward evacuation of sick and wounded shows two-stream triage by medical regulating officer at medical company (MED CO). Return to duty (RTD) patients are sent to combat support hospital (CSH) and non-return to duty patients to evacuation (EVAC) hospital. Area support medical battalion (AREA SPT MED BN) is convalescent unit for RTD patients in combat zone or communications zone (COMMZ). Medical aidman (MEDIC), soldier within unit, first triages to battalion aid station (BAS). AXP — ambulance exchange point, GEN — general hospital.

battalion [ASMB]). The ASMB is found at the CZ or the COMMZ level of care. Patients accepted from a medical clearing company (Fig 2) at the unit or division level are triaged into a two-channel stream to an EVAC hospital or CSH depending on the severity and the prognosis of the injury and the convalescent time. Transportation to the CSH would primarily be ground ambulance because of location within the CZ, while transportation to the EVAC hospital would rely on US Army and US Air Force air resources.

The key link in this evacuation system is early medical regulating and would require physician triage at an early level of care to separate an RTD from a non-return to duty (NRTD) patient. The severity of the patient's injury dictates the evacuation mode and final hospital destination according to a category of precedence (urgent, priority, or routine). Service capabilities of the various hospitals are as follows.

Combat Support Hospital. The specialties of general surgery, orthopedic surgery, ophthalmology, emergency medicine, internal medicine, dermatology, and obstetrics-gynecology are represented, as well as a dental section consisting of a dental officer and an oral surgeon. This hospital staff provides early diagnosis and treatment for a potential RTD patient.

Evacuation Hospital. Staffing would include a larger number of emergency physicians, general surgeons, and orthopedic surgeons, an ophthalmologist, an otolaryngologist, a thoracic surgeon, and a neurosurgeon, as well as a dental officer and an oral surgeon. This hospital provides stabilization for further evacuation of the injured soldier to the general hospital, or definitive medical or surgical care that ensures an RTD status within the evacuation policy of this hospital.

General Hospital. This level adds additional specialty provisions for an infectious disease officer and a urologist. This hospital also can provide for further evacuation of the injured soldier to CONUS.

Zone of Interior. The military health care system in the United States would provide beds for RTD patients expecting a convalescent period to a maximum of 60 days. Civilian and Veterans Administration beds are used for long-term patients who would not be expected to return to duty or need greater than a 60-day maximum for convalescence. These latter hospitals would be staffed by military hospital personnel, reservists, individual augmentees, draftees, new enlistees, and retired recalls, and would provide for the most definitive medical care available within the Army Medical Department system.

AIRLAND BATTLE TRIAGE OF TYMPANIC MEMBRANE PERFORATIONS

With this preceding general information, the following discussion of tympanic membrane injuries is given in order to focus on the consequences of evacuation of the soldier with blast injuries of the ear.[5] Approximately 88 days are lost for the surgical repair of this injury.

The Quad Service Clinical Data Base[6] recommends that patients with ruptured, lacerated, perforated tympanic membranes with severe involvement of the middle ear ossicles be transferred to CONUS for reconstructive ear surgery. Only 1 day of hospitalization is provided at the CZ level, and 2 days at the COMMZ level. Surgical equipment guidelines under this current doctrine mandate that operating microscopes be available only at the general hospital level in the COMMZ and that they be placed in a special equipment augmentation package. Microscopes are considered to be nonsupportable in the CZ (CSH and EVAC hospital) because of mobility limitations. Early medical evaluation and care of this injury therefore is limited at the CZ level because of the absence of an operating microscope. Confirmation of injury can be done only at the general hospital level prior to potential transfer to CONUS.

A patient with a moderate laceration or perforation involving only the drum spends approximately 7 days at the EVAC hospital, where an otolaryngologist provides care. Care consists of a paper patching and instituting water precautions. Audiometric analysis is unavailable at this level, so only clinical evaluation and tuning fork tests could be done by the otolaryngologist. This patient would be expected to return to duty within a 30-day period.

SUMMARY

Staffing an otolaryngologist at the EVAC hospital without the benefit of a microscope or audiometric testing equipment would probably limit early diagnosis and treatment of blast injuries of the ear and require further evacuation of the patient to a general hospital. The diagnosis of temporary threshold shifts or functional deafness, as well as pain, infections, or balance disturbances, generally would require further treatment at a more sophisticated hospital level with audiometric and microscopic support.

The functional consequences of a simple blast injury, with some exceptions, generally allow the soldier to complete the combat mission. It is unknown how many patients referred to a general hospital for diagnosis with specialty equipment might be returned to duty after a short convalescence. The implications of providing early and definitive health care treatment for blast injuries by an otolaryngologist would certainly need to be evaluated in the future relative to the priority of other battlefield injuries.

MEDICAL FORCE 2000

The Surgical Consultant to the Office of the Army Surgeon General, Colonel J. S. Parker, MC, USA, has provided the following update (personal communication, Jan 19, 1989).

"Since the presentation of this paper in 1986, the Army Medical Department is transitioning to a concept of combat medical and surgical care called 'Medical Force 2000.' During this transition, the composition of the professional staff of the Combat Support Hospital has been changed to include an Otolaryngologist/Head and Neck Surgeon supported with appropriate equipment. This will give the soldier otolaryngic specialty care in the Corps Area. This will effect reduction of the evacuation, evaluation and treatment time and permit us to return the majority of soldiers with barotrauma (otic) to duty within the limits of the expected evacuation policy.

"Otolaryngic specialty augmentation is available through the use of a 'Head and Neck Surgery Team.' This team can be attached to any facility that has the basic otolaryngology equipment capability.

"Current doctrine and policy recognizes the Otolaryngology/Head and Neck Surgeon as an important member of a trauma care team."

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BLAST INJURY OF THE EAR: HISTORICAL PERSPECTIVE

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Blast injury of the ear is rarely encountered by the practicing otolaryngologist. The recent world literature on this entity is reviewed. Symptoms, patterns of injury, and clinical course are highlighted and should form the basis of management under acute and chronic circumstances.

KEY WORDS — blast injury, ear, hearing.

Blast injury of the ear is an uncommon injury, seldom seen by the practicing otolaryngologist. It is most commonly seen in the setting of violence, in acts of war, and occasionally in industrial accidents. Most of the current reports have come from studies of such occurrences and will be discussed in detail.

The first report of deafness following blast injury in the medical literature is credited to Green[1] (1872). Since then, only sporadic reports have appeared. This review will focus on the more recent reports. Data from World War II (WW II) casualty studies[2] reveal that aural casualties represented 5.8% of 36,000 surgical patients treated at the 108th General Hospital in Paris. Tympanic membrane perforations account for 36.7% of all aural casualties. Diseases of the ear and mastoid were the sixth most common cause of loss from duty, after psychoneurosis, malaria, gonorrhea, hepatitis, and other infections. The usual policy in WW II was to evacuate soldiers whose hearing was below a serviceable level and might have created a hazard to themselves or their fellow soldiers. Such soldiers were reassigned to noncombat units. Hearing aids enabled some affected soldiers to remain in the theater of war who would otherwise have been evacuated.

Kerr and Byrne[3,4] and Kerr[5,6] reported on the otologic injuries in the March 1972 explosion of a small bomb in the crowded Abercorn restaurant in Belfast, Ireland, affecting over 80 persons. Two people were killed, several lost limbs, and others suffered various other serious injuries. The authors attributed the high number and severity of the injuries to the confined space in which the explosion occurred. Pahor[7] reported the otolaryngologic findings in 41 of the 111 survivors of the November 1974 bombings of two crowded public houses in Birmingham, England. Twenty-one persons were killed. Ruggles and Votypka[8] reported 11 tympanic membrane perforations in seven persons injured in the February 1970 bombing of the Shaker Heights, Ohio, police station. Singh and Ahluwalia[9] reported otologic injuries seen during the Indo-Pakistan conflict of 1965. Ziv et al[10] reported otologic injuries seen in two explosions: the sinking of a destroyer by missiles in October 1967 and the explosion of a truck carrying explosives in January 1970. Pratt et al[11] performed auditory brain stem response audiometry (ABR) studies of 37 soldiers following blast injury. Sudderth[12] reported abnormalities encountered in the course of 107 tympanoplasties for tympanic membrane ruptures subsequent to blast injuries from the Vietnam conflict.

The most common symptoms following blast injury of the ear are hearing loss, tinnitus, pain, and dizziness. In Kerr and Byrne's[3,4] and Kerr's[5,6] Belfast series, hearing loss occurred frequently. Almost all patients in the restaurant reported severe hearing loss immediately after the explosion. Although this resolved rapidly in most, usually within a few hours, others had permanent losses. A year or more after the explosion, 30% had high frequency sensorineural hearing loss greater than 30 dB at 4,000 and 8,000 Hz in one or both ears. In nine patients (10%), the speech frequencies were affected as well. Only 5% of patients were affected seriously as defined as a hearing loss of at least 40 dB for the speech frequencies in both ears. All of these patients had tympanic membrane perforations.

Pahor[7] found that deafness occurred in 25% of patients immediately after the Birmingham explosions. Those nearest the explosion, and ears facing the explosion, suffered the worst effects. Although deafness improved within hours, the sensorineural hearing loss took several months to recover or

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TYMPANIC MEMBRANE PERFORATION

	Kerr & Byrne,[3,4] *Kerr*[5,6]	*Pahor*[7]	*Ruggles & Votypka*[8]	*Singh & Ahluwalia*[9]	*Ziv et al*[10]	*Pratt et al*[11]
No. of patients	101	111	7	41	77	37
No. of perforated tympanic membranes	66	29	11	52	82	39
Percentage of ears with perforations	33	13	79	63	53	53
Percentage of ears spontaneously healed	83	82	*	78	88	†

*All repaired surgically.
†Not reported.

stabilize. The audiometric pattern in persistent loss was similar to the initial pattern.[7]

Ziv et al[10] found hearing was normal 1 to 3 years after the injuries in 91 ears (60%); conductive hearing loss was present in eight ears (5%); mixed hearing loss in 11 ears (7%); flat or sloping sensorineural hearing loss in nine ears (6%); and high frequency sensorineural loss (400 Hz) in 35 ears (22%). Thus, a total of 35% of ears were left with some sensorineural hearing loss.

Pratt et al[11] found ABR to be of value in the evaluation of blast injury of the ear. They examined 35 soldiers who were victims of a truck bombing, side-charges, rocket-propelled grenades, or landmine explosions. Twenty-six of the 37 soldiers (70.3%) suffered 39 tympanic membrane perforations in 74 ears (52.7%). Pure sensorineural hearing loss was found in 44.6%, pure conductive loss in 6.8%, and mixed hearing loss in 41.9%. The ABR findings were correlated with the components and types of hearing loss and with the prognosis for recovery. The conductive component was associated with prolongation of all peak latencies. Temporary threshold shift was associated with prolongation of peak I latency beyond that due to the conductive component. Permanent threshold shift was associated with no latency prolongation. The greater the prolongation of peak I latency, the better the prognosis for improvement of hearing.

Several recent studies have addressed hearing loss sustained during combat. In a study of 338 soldiers with hearing loss sustained during the Falkland Islands campaign, Brown[13] divided patients into three groups by the type of exposure: 179 operators of support weapons (mortars, artillery, etc), 109 infantrymen using personal weapons (small caliber), and 50 Welsh guardsmen who were survivors of blast injuries from the bombing of the *Sir Galahad*, June 8, 1982. Moderate to severe hearing loss was found in 15.7% to 23.7% of the support weapons group, 7.3% of the personal weapons group, and 18% of the Welsh guardsmen. The authors concluded that those using heavier weapons are at greater risk and that the mean hearing loss was 5.1 dB in the right ear and 5.5 dB in the left ear. They also found that compliance with hearing protection was so poor that no conclusions could be made regarding its effectiveness. This was a controlled study, since precampaign hearing levels were known.

Melinek et al[14] studied 433 soldiers from combat units with hearing loss and/or tinnitus. Of the 866 ears examined, 16.2% were normal, 14.3% had mild acoustic trauma, 41.9% had moderate acoustic trauma, and 27.6% had severe acoustic trauma. Two groups were studied: those transferred to a less noisy environment (ie, noncombat units) and those remaining in the noisy environment (ie, combat units). In the former group, 30.8% improved and 4% deteriorated. In the latter group, only 8.7% improved, while 30.4% deteriorated. The authors concluded that 1) the best treatment is prevention (ie, proper use of earplugs, earmuffs, or helmets), 2) removal from the noisy environment has beneficial effects, and 3) remaining in the noisy environment (combat unit) has deleterious effects.

In a second study from the Falkland Islands conflict, Anderson[15] found that 50% of 114 soldiers in the Royal Artillery showed mild deterioration of hearing (H1 to H2 category) and 15% showed moderate to severe deterioration (H3 or greater). They concluded that despite exposure to very high levels of impulse noise, the large majority either have been unaffected or have had minimal changes and required no restrictions or limitations of duty.

Tinnitus was found in 23% of patients in Pahor's report[7] and was a very common complaint in the Kerr and Byrne[3,4] and Kerr[5,6] reports. Tinnitus tends to parallel sensorineural hearing loss and generally resolves with resolution of the hearing loss. Pain was not a common complaint, being reported by only 1% of patients in Pahor's report, although most patients reported pain when specifically asked. Dizziness was uncommon, occurring in only 1% of patients in his report. According to Kerr and Byrne, vertigo usually is associated with significant closed head injury when it does occur. However, benign positional vertigo unrelated to other head injury has occurred following blast injury to the ear.[3,4,6]

Damage resulting from blast injury to the ear involves the tympanic membrane, cochlea, vestibular system, and ossicles. By far, the single most common injury reported is tympanic membrane perforation. Although the ear nearest the explosion usually is damaged more severely, the blast wave reportedly can ricochet off a nearby wall to damage the contralateral ear.[7] The pars tensa is the susceptible portion of the tympanic membrane. No damage to the pars flaccida has been reported. Overall, a 78% to 88% spontaneous healing rate has been reported. The Table[3-11] lists the incidence of tympanic membrane perforation and the spontaneous healing rate reported in the various studies.

The size of perforation appears to be related to the spontaneous healing rate. Singh and Ahluwalia[9] reported that 39 of 43 perforations involving less than one third of the tympanic membrane healed spontaneously. However, only two of nine perforations involving greater than one third healed spontaneously. Pahor[7] found that all perforations failing to heal spontaneously involved greater than 80% of the tympanic membrane. Conversely, all perforations less than 80% healed spontaneously. On the basis of these findings, it may be appropriate to use the size of the perforation as a criterion for surgical intervention.

It has been speculated that the edges of the perforation may be inverted or that squamous epithelium may be driven into the middle ear, resulting in formation of cholesteatoma. This should be considered in planning management of blast injury perforations.

Inner ear damage has been reported uncommonly. Strong[16] in 1973 reported a perilymphatic fistula in the oval window. Ruedi and Furrer[17] in 1947 found a case of dislocated stapes. Kerr and Byrne[3-6] reported ruptures of the saccule, utricle, and basilar membrane in a study of ten temporal bones from persons who died following blast injuries. Interestingly, they found no ossicular damage in those cases. Thus, it appears that ossicular damage is not a prerequisite to inner ear damage.

Ossicular injuries did not occur in either of the two largest studies: the Pahor report[7] of 111 patients and the Kerr and Byrne[3,4] and Kerr[5,6] reports of 101 patients. In Sudderth's study,[12] the most common ossicular abnormality was medial displacement of the malleus handle with disruption of the incudomalleal joint and adherence of the tip of the malleus to the promontory. This was found in 25% of cases. Of the incus and stapes abnormalities found in 8.4% of cases, incudostapedial joint separation (four cases) was most common, followed by incudostapedial joint separation with fracture of the stapes superstructure (one case). Messervy[18] reported a case of blast injury ossicular damage sustained when a shell burst 50 yards away from a soldier. The incudomalleal joint was dislocated and the incus was lying free in the hypotympanum. Both stapedial crura also were fractured.

Because it is the positive phase of blast overpressure that disrupts the tympanic membrane, one might expect squamous epithelium to be forced into the middle ear space, ultimately giving rise to cholesteatoma. Alternatively, the perforation edges might be folded inward, providing an avenue for ingrowth of squamous epithelium. Indeed, cholesteatoma has been found following blast injury perforations. Kerr and Byrne[3,4] reported two cases of cholesteatoma. Seaman and Newell[19] reported a case of cholesteatoma complicating a blast injury of the ear. It appears, therefore, that the otologic surgeon should provide long-term follow-up and surveillance for cholesteatoma.

To summarize, the most common symptoms of blast injury include hearing loss, tinnitus, pain, and vertigo. Tympanic membrane rupture is the most common physical finding. Ossicular damage is rare. Late sequelae may include persistent tympanic membrane perforation, permanent hearing loss, and cholesteatoma. Management of blast injuries of the ear should be based upon the known data and is covered elsewhere in this symposium.

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TREATMENT OF BLAST INJURY TO THE EAR

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Blast injury to the ear has long been acknowledged as potentially incapacitating. This paper discusses the scope of these injuries in terms of the anatomic and physiologic consequences. Management of both acute and chronic injuries is discussed, with specific regard to the deficits in a patient's functional ability once blast injury has occurred.

KEY WORDS — blast injury, ear, hearing.

In order to manage blast injury to the ear appropriately, an appreciation for the scope of otologic injury that may result from the blast is required. Varying degrees and duration of hearing loss, otalgia, tinnitus, and vertigo have been reported. Late manifestations of blast injury also have been noted and include permanent hearing loss, predisposition to infection secondary to perforation, and cholesteatoma.[1-4] We focus our discussion on the incapacitation resulting from blast injury, the immediate and long-term management of such injury, and the need for further research to improve our understanding of the problem.

Hearing deficits resulting from blast injury may be conductive, sensorineural, or mixed.[3] A conductive loss usually is caused by a tympanic membrane rupture, although ossicular damage and serous otitis have been seen after blast exposure.[2,4] Sensorineural losses from inner ear damage may range from temporary threshold shifts, in which transient disruption of cochlear function is suspected, to a more permanent loss from labyrinthine fistulas, basilar membrane ruptures, or other defects.

As little as 2.25 kg/cm^2 (5 lb/in^2) of force may produce tympanic membrane rupture, and at 6.75 kg/cm^2 (15 lb/in^2), 50% of adult tympanic membranes will perforate.[5,6] Tympanic membrane rupture occurs in up to 32% of all casualties from terrorist bombings. The incidence is higher (to 63%) in those admitted to hospitals following a blast.[7] The resultant conductive hearing loss will depend on the size and location of the perforation. It previously was thought that the presence of a perforation meant incapacitation of the injured individual. This has been disputed, however, since many patients can maintain an excellent level of function with perforation, provided no other incapacitating injuries are received from the blast.[8-10]

SYMPTOMS

Sensorineural hearing loss, often accompanied by tinnitus, frequently is reported after blast injury. The sensorineural loss may be the most incapacitating symptom of the injury in the immediate postblast period. The loss, more prevalent in the high frequencies, also may affect speech frequencies. The potential impairment of hearing is greater than that caused by middle ear damage. Severe sensorineural loss in the postblast period compromises a person's ability to communicate and seriously disorients him or her with respect to the immediate environment. Unaware of the deficit, the person may notice the loss only when he or she sees people talking but hears little or no sound.[11] This type of loss usually resolves within the first few hours, but permanent loss may occur in up to 30% of victims.[1,3,7,12] The course of tinnitus tends to parallel that of the sensorineural loss, resolving within a few hours in most cases.

Temporary threshold shift is presumed to be secondary to a reversible biochemical cochlear dysfunction. Other causes of sensorineural loss include perilymphatic fistula, loss of hair cell integrity, and rupture of labyrinthine membranes; these injuries likely would result in a permanent loss.

Vertigo or dizziness after blast injury has been reported and seems to be associated with head injury from secondary or tertiary blast effects rather than with the primary blast effect.[1,11] Significant vertigo, dizziness, or gait instability related to associated head injury is likely. These more serious injuries require more sophisticated evaluation than a cursory examination can provide.

Otalgia after blast may have many causes, including eardrum rupture, ossicular disruption, or concussive injury from other blast effects. In cases

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of middle ear drainage it is unlikely that the otalgia will be incapacitating.

TREATMENT

Injuries that lie between the very severe and the uncomplicated small isolated tympanic membrane rupture will require individual disposition. Very few guidelines are available to assess levels of functional incapacitation. This area needs further research, but some general guidelines may be offered. In cases of simple perforation, water precautions should be observed. Patients with severe sensorineural loss should avoid high noise levels, and they should be assigned to duty that does not require sensitive hearing.

In a combat setting a patient evacuated for further therapy would come under the care of an otolaryngologist at the evacuation or general hospital level. A rational approach to evaluation and treatment of blast damage to the ear requires an understanding of the natural history of the injury. Follow-up of patients with blast injury shows spontaneous resolution rates of 82%, 88.4%, 81%, and 91%.[6,7,11-13] Some factors affecting the chances of healing are as follows:

1. Location. Posterior superior perforations are associated with retraction pockets and/or cholesteatoma in a number of cases.[14]
2. Size. Perforations larger than 30% of the total tympanic membrane surface have a significantly lower rate (0% to 22% of affected ears) of spontaneous healing.[11,15] Size also affects the rate of healing. Pahor[11] states that 1 month is required to heal each 10% of perforation.
3. Time postinjury. Many studies show that if no healing has occurred in 10 to 15 days, further spontaneous healing is unlikely to occur.[1,14] Others advocate a longer waiting period (to 6 months).

The late sequelae of blast injury have not been as well documented. Cholesteatoma has been reported in several series, though its incidence has not been documented. Sudderth[4] predicted that cholesteatoma was likely to be the most important late complication in these injuries.

Hearing loss may be a late complication in a significant number of patients. Ziv et al[12] followed up on 154 ears in 77 individuals injured on a destroyer hit by missile fire and those injured in an explosion of a nearby munitions truck. Patients were observed from 1 to 3 years, and anyone with a previous hearing loss was excluded from the study. Forty-four ears (29%) showed residual sensorineural hearing loss, 11 (7%) showed a mixed loss, and eight (5%) showed a persistent conductive loss.

Examination of middle ear spaces following blast injury has shown tympanic membrane fragments embedded in middle ear mucosa. The edges of perforations frequently are inverted under the remaining portion of eardrum. These findings suggest that the positive phase of the blast wave is responsible for membrane rupture. This implosive splaying of tympanic membrane fragments may explain cholesteatoma formation following blast injury to the ear.[1,2]

The management of blast injury may be divided into immediate and long-term care and will differ in combat and noncombat scenarios. In the immediate postblast period, assessment must be made of the patients' other injuries, since otologic injury may be relatively minor. Fractures, penetrating wounds, lacerations, and burns frequently are seen in the blast victim. It is essential that the principles of triage and trauma management be executed properly. Further details of otologic injury may be sought once the patient's condition has stabilized. The examiner should investigate such details as the proximity of the victim to the blast; the type of munitions encountered; the orientation of the head to the blast; the presence of tinnitus, otalgia, or bleeding from the ear; and the pressure of blockage sensation. Of historical and prognostic value is the presence or absence of a preexisting hearing deficit. The time course of the hearing loss and any spontaneous resolution must be noted and, where possible, documented audiometrically.

An otologic examination should be performed as soon as possible. An accurate description of the size and location of any perforation should be recorded, and the hearing level assessed by any subjective or objective means available. The presence of foreign material in the ear or dislocation of ossicles should be noted.

The management of otologic blast injury may differ dramatically depending on the situation in which it occurs. Ideally, everyone sustaining otologic blast injury will be evaluated by an otolaryngologist who, using a combination of subjective and objective information and audiologic and microscopic examination, will devise a treatment plan suited to each individual case. This luxury is unlikely to be present in wartime.

Isolated blast injury to the ear sustained by a soldier in combat will need to be evaluated relative to his or her ability to continue the combat mission. Assuming no other disabling injury has been incurred, an assessment is made of the degree of incapacitation caused by the blast. Certainly a small perforation of the tympanic membrane with no subjective hearing deficit would not require transfer to an evacuation hospital, given the likelihood of spontaneous healing within a couple of weeks. On the other hand, a severe hearing loss imposed by a significant temporary threshold shift may render an individual nonfunctional in a situation in which communication is essential in order to perform a mission, or in which lives may depend on ability to detect subtle sounds. Hence, medical personnel involved in initial triage and screening must assess incapacitation on the basis of both subjective and objective data.

The following guidelines are defined in order to make appropriate assessments. Absolute indications of functional incapacitation have not been described in the literature of military medical doctrine.[16] Situations that might apply to that category would be 1) total loss of hearing, 2) total or near-total loss of the tympanic membrane, 3) ossicular damage, and 4) severe vertigo or loss of balance. Temporary threshold shifts probably will produce the majority of severe hearing losses. Observation at an aid station for several hours or overnight will allow time for most patients to improve. A patient with a persistent severe loss being considered for evacuation should be evaluated for a hysterical component.

Closure of isolated perforations may be attempted on the basis of size. Perforations of less than 30% of the surface area of the tympanic membrane will heal spontaneously in most cases, and the individual will return to duty in which acute hearing is not critical and water precautions can be followed. Otologic follow-up at the earliest possible time is recommended. Perforations greater than 30% would be less likely to heal spontaneously. Definitive tympanoplastic surgery is indicated.

Ossicular damage, by nature, implies a more severe injury and is manifested by a significant conductive component. Evacuation is indicated, since a person with this damage is unlikely to have adequate hearing in the ear and usually has suffered other major traumatic injuries.[6,17] Significant vertigo, dizziness, or gait instability may also be caused by a severe blast injury. The likelihood of associated head injury is high. These factors combine to make this a serious injury that will require evacuation.[5,17]

Several options are available in the treatment of serious blast injuries, including observation, paper or Gelfilm patching, and tympanoplasty with fascial grafting with or without ossicular reconstruction. Dextran or steroid therapy has been used in treating the sensorineural loss.[1]

One approach advocated by several authors is first to anesthetize the ear locally, then clean the ear and remove fragments of tympanic membrane from the middle ear, if present. Torn edges are everted and reapproximated under sterile conditions. A Gelfoam bed is laid in the middle ear for support, and a patch of Gelfilm or paper then is applied over the perforation. Rates of healing with this method are consistently over 90%.[6] Advantages of this approach include correction of the lost baffle effect (since the round window protection will allow a phase difference between oval and round windows) and creation of a greater tympanic membrane surface. The possibility of late cholesteatoma also may be lessened by debridement and eversion of torn membrane edges.

Variations of treatment include trichloroacetic acid cautery of edges in late perforations (ie, those that have failed to heal spontaneously), relaxing incisions to permit better approximation of edges, and fascial grafts instead of paper or Gelfilm patches.[14] Tympanoplasty with a medially placed fascial graft alone has a greater than 90% success rate. This method of repair is used for long-standing perforations (3 to 6 months) or in failed attempts at patching.[1] Antibiotics and ear drops are recommended for use only when infection or drainage is present.[5]

SUMMARY

Blast injuries of the ear have various sequelae. Proper management includes appropriate initial triage for major traumatic injuries. Small tympanic membrane perforations are expected to heal spontaneously. Larger perforations in the presence of severe hearing loss, ossicular damage, vertigo, gait instability, or dizziness following blast injury merit further evaluation. Audiologic follow-up is warranted in all cases when practical. Water precautions are essential when a perforation is present. Further research is needed to determine levels of incapacitation under specific injury situations. In a military setting, research is also necessary to design ear protection that will afford blast protection but not significantly compromise mission performance.

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MIDDLE EAR INJURY IN ANIMALS EXPOSED TO COMPLEX BLAST WAVES INSIDE AN ARMORED VEHICLE

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With greater reliance on armored vehicles of improved survivability, questions have arisen about the likelihood of the wounding of vehicle occupants from blast waves alone. In this study, we placed anesthetized animals (sheep or pigs) inside lightly armored vehicles and exposed them to the blast waves generated by one of three sizes of shaped-charge munitions. Sixty-seven animals were exposed and 15 served as controls. No difference was noted between exposed and control groups for blast injury to the respiratory or gastrointestinal tracts. In contrast, middle ear damage was observed exclusively in animals exposed to blast and was correlated strongly with the peak pressure. The ear is the organ most sensitive to blast damage, and if protectors are not used, military physicians can expect to see a high incidence of middle ear injury in modern combat. The operational consequences of such an injury are not known.

KEY WORDS — blast injury, military medicine, tympanic membrane rupture.

The modern battlefield is centered around the varied roles of armored combat vehicles (ACVs). In the armored battles of northern Europe during World War II and during the more recent Middle East conflicts, tank crews sustained 1.5 to two casualties when struck by penetrating anti-armor munitions.[1] A similar number of injuries were reported in the US experience in Vietnam (where mostly small caliber munitions were used) in both armored personnel carriers and tanks.[2] The vast majority of these combat casualties were due to wounds from fragments and burns. Now, ACV design has advanced significantly and it is possible to construct a vehicle in which both the crew and the vehicle itself are much more likely to survive a strike by anti-armor munitions and to continue as a fighting unit.[3]

Current US infantry carriers are shielded by aluminum armor. Aluminum offers greater ballistic protection than an equal weight of steel.[3,4] However, concern has been expressed that the use of aluminum may pose a hazard to crews.[5] When any armor is penetrated by a shaped-charge munition, also called a high explosive antitank (HEAT) round, part of the armor material is vaporized or broken into fine particles. Some of the pieces of the penetrating munition and the vehicle's armor itself (called spall) are thrown into the vehicle interior and cause fragment wounds. In addition, the finely dispersed metal offers a large surface area for rapid oxidation that may result in an increased temperature and pressure pulse within the vehicle, analogous to a grain dust explosion. This exothermic reaction is termed the vaporific effect and it has been reported to be particularly energetic when aluminum is penetrated. It has been suggested that the vaporific effect behind aluminum armor is so destructive that it poses a serious threat to ACV crew members who might otherwise not be injured by fragments or fire from a penetration.[3,5] In an attempt to define this risk to soldiers, the US Army undertook an evaluation of the effects of blast waves inside lightly armored aluminum ACVs penetrated by HEAT munitions.

MATERIALS AND METHODS

Blast injuries were assessed inside light, aluminum armored infantry carrier vehicles that are currently in use with US Army units. Both the M113 Armored Personnel Carrier and the M2 Bradley Infantry Fighting Vehicle were used. Results from both vehicles are pooled in this report. The vehicles were struck with either a large shaped-charge munition characteristic of antitank guided missiles (US TOW, Soviet Sagger or European Milan class) or a smaller HEAT round of the size found on light, shoulder-launched antitank weapons (US LAW, Soviet RPG or European Karl Gustav class). These munitions are denoted hereinafter as either the large threat or the small threat, respectively. The results from one test round per vehicle of a cannon-fired medium caliber HEAT munition is included in the large threat category. The vehicles were ballistic hull and turret configurations, ie, they had all

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From the Department of Respiratory Research, Walter Reed Army Medical Center, Washington, DC. The views or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense. In conducting the research described in this report, the investigators adhered to the standards set forth in the *Guide for the Care and Use of Laboratory Animals* (NIH publication) as promulgated by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council.

Presented at the Blast Injuries of the Ear Seminar, sponsored by the Department of Respiratory Research, Walter Reed Army Institute of Research, and the Otolaryngology–Head and Neck Surgery Service, Walter Reed Army Medical Center, Washington, DC, Sept 26-27, 1986.

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of the external armor and the interior dimensions of a standard combat vehicle but did not have engines or other working electronic systems. In order to isolate the effect of the blast associated with the penetration event from other possible casualty mechanisms, no ammunition or fuel was placed in the vehicles.

Mixed breed sheep (41) and pigs (41) of both sexes weighing 25 to 40 kg were used. Previous work has shown that pigs and sheep of the same size have essentially identical responses to blast waves.[6,7] Twenty-four hours prior to exposure, animals were selected at random, segregated from the other animals, held off feed, and allowed water free choice. The day of exposure the selected animals were placed in individual stainless steel cages and transported in a well-ventilated, covered vehicle approximately 32 km to the test site. Continuous animal care was under the direct supervision of veterinarians. Thirty minutes prior to being placed in the test vehicle, the anesthetic regimen for the pigs was initiated. The regimen for the sheep was started 5 minutes before placement in the vehicle.

Because of the nature of the study, it was necessary to have a parenteral anesthetic regimen that would provide up to 1 hour of pain-free restraint without supplementation and would not require tracheal intubation. Drug regimens were developed prior to the initiation of this study and found to provide the required anesthetic efficacy with no thermoregulatory or cardiopulmonary complications.[8,9] The desired level and length of pain-free restraint for the pigs was provided with an intramuscularly administered preanesthetic-anesthetic combination beginning 30 minutes prior to placement with azaperone (Stresnil), 2.2 mg/kg body weight, and 100 mg meperidine hydrochloride (Demerol). Twenty minutes later, 10 mg morphine and ketamine hydrochloride (Ketaset), 2.2 mg/kg body weight, were administered intramuscularly. The anesthetic for the sheep was much simpler, comprising only the intramuscular injection of xylazine (Rompun, 100 mg/mL) at a dose of 1.1 mg/kg body weight.[9]

Once anesthetized, the animals were placed in fishnet support slings equipped with custom leg fenestrations. They then were suspended in the test vehicle in predetermined positions from support hooks hanging from the roof of the vehicle. The slings kept the animals in the desired position and posture without impeding normal thoracic or abdominal motion. Each animal's position was predetermined by a randomized design. Animal locations were chosen to simulate normal crew positions away from the area in which fragment injuries were expected.

After all animals were positioned, the hatches were sealed, and between 5 and 15 minutes later, the test munition was fired into the vehicle. The aim point was the same for all shots on the M2 and the M113. Thirty-six animals were exposed to the small threat and 31 were exposed to the large threat. Approximately 3 minutes after the round was fired, the animals were removed from the vehicles and carried to the transport vehicle. Animals that showed signs of arousal from anesthesia at any time were given booster dosages of the respective drug regimens (only morphine-ketamine in pigs). This assured adequate pain-free transportation back to the laboratory. The animals were transported in the same vehicle in separate cages and monitored closely.

The pressure environment inside the vehicle was recorded using Endevco piezoelectric pressure transducers flush mounted on the vehicle walls near the positions of the animals. The relative orientations and distances of the probe sensing surface with respect to the animals' ears at the time of exposure are unknown. Gauges were always within a meter of animal positions. The signals were acquired at 250 kHz and filtered at 40 kHz. A custom software package determined the peak pressure and pressure impulse for each record. The latter is the integral of the pressure-time signal taken, in this circumstance over the first 2.1 ms of the blast event. For freefield (ie, nonreverberant) blast waves, this integration interval has been shown to correlate with injury to human-sized animals.[6]

Eight pigs and seven sheep served as controls. These animals were subjected, three or four at a time, to the procedures as described with the exception of the firing of the antitank round. These animals underwent the same environmental, transportation, anesthetic, and restraint stresses as their experimental counterparts.

Euthanasia of the anesthetized test animals was achieved by rapid intravenous injection of an overdose of barbiturate. Animals were necropsied 2 to 5 hours after exposure. All necropsies were supervised by a board-certified veterinary pathologist. Thorough external and internal gross examinations were performed on all tissue and organs from all animals, with emphasis on inspection for tissue changes characteristic of blast-related injury. This report emphasizes injury to the middle ear. Damage to nonauditory structures is addressed only briefly, and the full details of the necropsy protocol are given elsewhere.[7]

During the necropsy, the temporal bones were dissected and the middle ear was exposed. The tympanic membrane and ossicular chain were examined for gross damage with the injury evaluation scale below. Injuries having involvement of the ossicles were considered to be more severe in nature (categories 4 and 5). The inner ear structures were examined in great detail as reported by Roberto et al elsewhere in this Supplement (p 23).

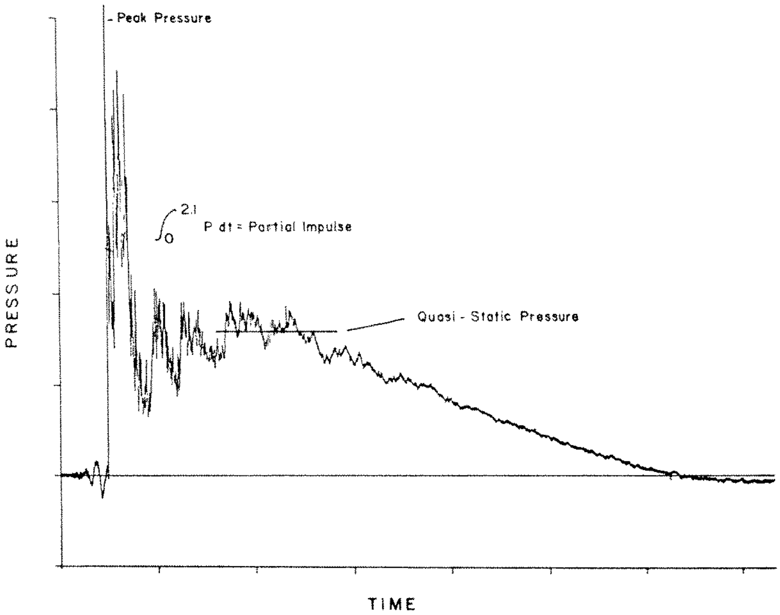

Fig 1. Typical pressure-time history observed inside lightly armored combat vehicle following penetration (of armor only) by high explosive antitank munition. Peak overpressure, partial impulse, and quasistatic overpressure can be used to assess hazard of injury.

The injury evaluation scale had six gradations: 0 — normal; 1 — small blood clot on tympanic membrane, usually at the attachment of the malleus, no tears; 2 — small tear at the attachment of the malleus; 3 — large tear or rupture, usually at the tip of the manubrium of the malleus; 4 — fracture of the manubrium of the malleus and one or more tears of the tympanic membrane; and 5 — disarticulation of stapes from the oval window. Statistical comparisons between groups of animals exposed to different conditions were made by χ^2 analysis,[10] with p values of $< .05$ considered to indicate significant differences between outcomes. Linear regression was accomplished with the Statistical Analysis System.

RESULTS

Because of the variation in geometry within the test vehicles, there was considerable variation in the pressure environment. The large test round resulted in mean overpressures in the crew compartments of 154 ± 66 kPa (± 1 standard deviation) for 27 observations. The impulse (integral of pressure-time signal) over the first 2.1 ms of the event averaged 163 ± 43 Pa·s. The small test round averaged 41 ± 21 kPa and 43 ± 18 Pa·s. Figure 1 depicts a typical pressure tracing from a large threat round penetration.

Blast injury to organs other than the ears was minimal. Trivial lesions of the lungs consistent with blast injury were observed in two of 36 animals exposed to the small threat, one of 31 animals exposed to the large threat, and in none of the 15 control animals. The gastrointestinal tract showed a large colonic hematoma in only one animal exposed to the large threat.

The relative susceptibility of pig and sheep eardrums to rupture in a blast environment is unknown. The data from this study suggest that the sheep may be more sensitive, with 17 of 20 ears damaged in one subseries of the test as compared to only six of 16 pig ears injured in a similar exposure position within the same vehicle ($\chi^2 = 8.7$; $p < .005$). The trend continued but was not statistically significant in another crew position, with three of ten pig ears and eight of 16 sheep ears being injured ($\chi^2 = 1.00$; $p > .1$). All summary eardrum injury data in this paper are given for both species combined.

Of 70 ears subjected to small threat (one ear was not evaluable because of external canal occlusion), 25 ears (36%) were damaged, ie, had gross injury to the tympanic membrane or ossicles, and seven ears (10%) were damaged severely, ie, suffered fractures or disarticulation of the ossicles. Severe injury corresponds to grade 4 or 5 on the scale above. It is anticipated that such injury to the ossicles will require more extensive medical care than simple tears of the tympanic membrane and will have greater long-term sequelae. Of 71 ears subjected to large threat, 50 ears (71%) were damaged, 24 (34%) severely. As one would expect, exposure to the overpressure generated by the large threat resulted in a significantly greater incidence of both ear injury of any grade ($\chi^2 = 17$; $p < .005$) and severe ear injury ($\chi^2 = 11.6$; $p < .005$). The Table gives the incidence of middle ear injury as it correlated with specific ranges of peak pressure and pressure impulse, respectively.

Figure 2 is a histogram showing the incidence of total and severe injury for the range of observed peak pressures. Above 100 kPa the total incidence was nearly constant at 0.90 (see Table). Consequently, all observations above that level were grouped together. A linear regression was performed by use of the median value of each histogram bar (eg, 12.5 for 0 to 25 kPa and 37.5 for 25 to 50 kPa) and the incidence of injury (weighted for

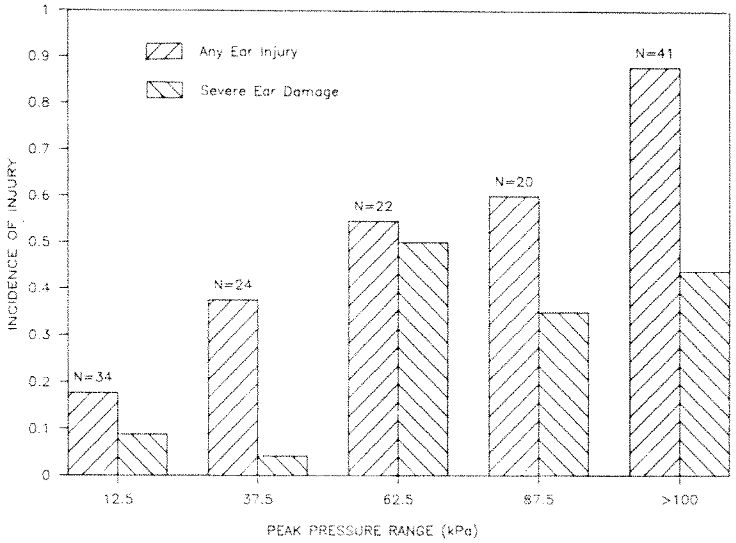

Fig 2. Incidence of both total and severe middle ear injury as function of peak overpressure for sheep and pigs inside penetrated light armored combat vehicles.

the number of observations for each pressure range). This was done for both overall and severe injury categories. All observations above 100 kPa were grouped together and weighted to 125 kPa. With these caveats, overall eardrum injury incidence could be described for any peak pressure up to 125 kPa as

$$I(\text{total}) = 0.00656\ (\text{pressure in kPa}) + 0.0765 \quad (r = .983)$$

and the incidence of more severe ear injury could be described as

$$I(\text{severe}) = 0.00382\ (\text{pressure in kPa}) + 0.2971 \quad (r = .824).$$

DISCUSSION

In contrast to the paucity of injury to the lungs and gut, eardrum rupture was noted very frequently inside these penetrated light ACVs. The eardrum is known to be very sensitive to overpressure.[11,12] The paper by Richmond et al (this Supplement, p 35) addresses the physical factors associated with eardrum and middle ear injury. Damage is known to be increased with increasing overpressure and rapid rise to peak pressure (rise time), and to vary with species, subject age, and orientation of the ear with respect to the blast wave. With long-duration nuclear-type blast waves, the eardrum may rupture at 30 kPa, whereas the onset of significant lung injury is at 300 kPa.[6,13]

In evaluating the risk of rupture inside a defeated ACV, one must consider both the initial overpressure events (Fig 1), which are probably responsible for any nonauditory injury, and the slower-rising quasistatic pressure rise (Fig 1). This latter pressure buildup is due to the presence of combustion gases and the heating of all of the gases inside the vehicle.[1] The pressure slowly begins to rise after 10 to 20 ms and, unless the hatches blow, can stay elevated for several hundred milliseconds. Work with slow-rising, long-duration nuclear pulses has indicated that eardrum rupture is dependent principally on peak plateau pressure. Thus, in the ACV, the relative importance of the sharp, short pressure pulses of penetration and the sustained quasistatic pressure to eardrum injury are not known. However, since the peak pressure was often much greater than the quasistatic plateau, it seems most likely that the initial explosive events are the most injurious.

Papers by Cassler et al and Chait et al (this Supplement, pp 13 and 9, respectively) deal in depth with the diagnosis and acute treatment of blast injury of the ear and the likely sequelae of such

INCIDENCE OF MIDDLE EAR INJURY IN SHEEP AND PIGS INSIDE PENETRATED LIGHT ARMORED COMBAT VEHICLES OBSERVED AT MEASURING POSITION NEAREST ANIMAL

	No. of Ears at Risk	*Ears Damaged**	*Ears Severely Damaged†*
Peak pressure range (kPa)			
0- 25	34	6	3
25- 50	24	9	1
50- 75	22	12	11
75-100	20	12	7
100-125	8	7	5
125-150	16	15	6
150-175	2	2	1
175-200	2	2	1
>200	15	12	6
Partial impulse range (Pa·s)			
0- 25	34	4	0
25- 50	32	15	5
50- 75	14	8	1
75-100	8	2	2
100-125	6	4	3
125-150	12	11	4
150-175	16	14	9
175-200	8	7	4
>200	11	10	3

*Gross injury to tympanic membrane or ossicles.
†Fracture or disarticulation of ossicles.

trauma. Basic treatment for a simple eardrum rupture consists of cleansing and use of antiseptic solution in the external canal.[12,14] Over 80% will close spontaneously; others may require surgery.[15] In general, such an injury would not require immediate attention in a combat setting. Care could be delayed for hours or even days without serious adverse consequences.

An important military consideration to such an injury in an ACV relates to its possible effect on a soldier's ability to perform his or her duties. This field trial points out the likelihood that many soldiers inside penetrated ACVs may be uninjured except for trauma to the ear. While eardrum rupture can be a painful event, if the tear is not severe the discomfort is tolerable and quickly subsides.[14,16] Indeed, tympanic membrane rupture is a frequent "incidental" finding in combat soldiers being evaluated for complaints of hearing loss.[17,18] With more extensive trauma resulting in hemorrhage or disruption of the ossicles, some incapacitation is possible.[16,19] A decrease in performance rarely may be due to persistent sharp pain or to disorienting tinnitus. Less frequently, the vestibular apparatus may be affected, with a resultant disabling loss of balance.[17]

Perhaps the most predictable result of such intense acoustic trauma is the induction of an acute hearing loss. This auditory decrement may range from minimal to massive and may be either temporary or permanent.[12,14,17,18] The paper by Roberto et al in this Supplement (p 23) documents the large amount of cochlear damage observed in the animals in this study. The effect of a profound loss of hearing acuity on military performance cannot be quantitated at present. However, many important military tasks require processing and acting upon aural information. Consider the surveillance functions of a night sentry or the job of a radio operator. During World War II, soldiers with major hearing losses were evacuated from the European theater of operations because they were "a menace to themselves and to their companions in combat."[18] It is safe to say that a soldier with a substantial loss of hearing acuity will be a less effective combatant. However, it is unlikely that aural injury alone would prevent a soldier from completing a combat mission.

The proper wearing of some form of hearing protection, including the US Army ACV crew member's communications helmet, should lessen greatly the risk of both eardrum rupture and hearing loss. Measurements made beneath such a helmet fitted to a solid dummy head inside penetrated ACVs have shown a decrease in measured peak pressure ranging from two to ten times that found in similar tests of the mannequin without the helmet. This potential degree of protection is supported by a Canadian study in which the average peak pressure beneath an earmuff of a mortar gunner was 162.4 dB (2.6 kPa) while the peak pressure in the air was 177.9 dB (15.7 kPa), a pressure reduction factor of six (15 dB).[20] A recent review by Forshaw and Crabtree[21] indicated that for heavy weapons noise, peak pressures measured at (or in) the ear were reduced by 11 to 21 dB for earphones and almost 30 dB for compressible foam earplugs.

In summary, this field trial demonstrated that soldiers inside light US Army ACVs who are outside the immediate zone of penetrating fragments are likely to suffer consequential blast injury only to their ears. The prevalence and severity of eardrum injury is greater for large anti-armor munitions and correlates positively with increasing peak overpressure. Such an injury may impair some aspects of military performance, particularly those involving critical aural tasks. Significant injury to the ears probably can be prevented by the proper wearing of standard hearing protectors.

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DAMAGE OF THE AUDITORY SYSTEM ASSOCIATED WITH ACUTE BLAST TRAUMA

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This paper reviews the results of several studies on the effects of blast wave exposure on the auditory system of the chinchilla, the pig, and the sheep. The chinchillas were exposed at peak sound pressure levels of approximately 160 dB under well-controlled laboratory conditions. A modified shock tube was used to generate the blast waves. The pigs and sheep were exposed under field conditions in an instrumented hard-walled enclosure. Blast trauma was induced by the impact of a single explosive projectile. The peak sound pressure levels varied between 178 and 209 dB. All animals were killed immediately following exposure, and their temporal bones were removed for fixation and histologic analysis using light microscopy and scanning electron microscopy. Middle ears were examined visually for damage to the conductive system. There were well-defined differences in susceptibility to acoustic trauma among species. However, common findings in each species were the acute mechanical fracture and separation of the organ of Corti from the basilar membrane, and tympanic membrane and ossicular failure.

KEY WORDS — chinchilla, cochlea, blast trauma, tympanic membrane.

INTRODUCTION

The auditory system evolved to detect naturally occurring low-level stimuli important for survival. Exposure of the auditory system to blast waves is perhaps the most unnatural of all "acoustic" stimuli that could be applied to this structurally most delicate of all organs. Hudspeth[1] makes the point that the cochlea, with over 10^6 moving elements, is the most complex mechanical system in the body. Since the peak sound pressure levels (SPLs) of blast waves frequently approach or exceed 200 dB, all mechanically driven parts of the auditory system are ultimately at risk, ie, the middle ear conductive structures and the cochlea. A secondary complication may include degenerative changes in the central auditory pathways.[2] This paper will focus on the mechanical damage to the conductive system and the sensory structures of the inner ear. There are comparatively few experimental studies of middle ear trauma in which an attempt was made to relate the exposure variables to the nature of injury following a severe acute noise exposure. White et al[3] carried out an extensive series of studies using several species (dog, goat, guinea pig, rabbit, etc) and a number of different wave configurations. A significant finding, which also points out a traditional problem in impulse noise research, was the extreme variability within species that made it difficult to relate the degree of trauma to specific exposure variables. However, in addition to the peak SPL, the rate of pressure increase and the duration of the waveform would appear, from the data of White et al, to be important variables in the production of a tympanic membrane rupture. A number of other studies of this genre appeared in the post-World War II period, often associated with

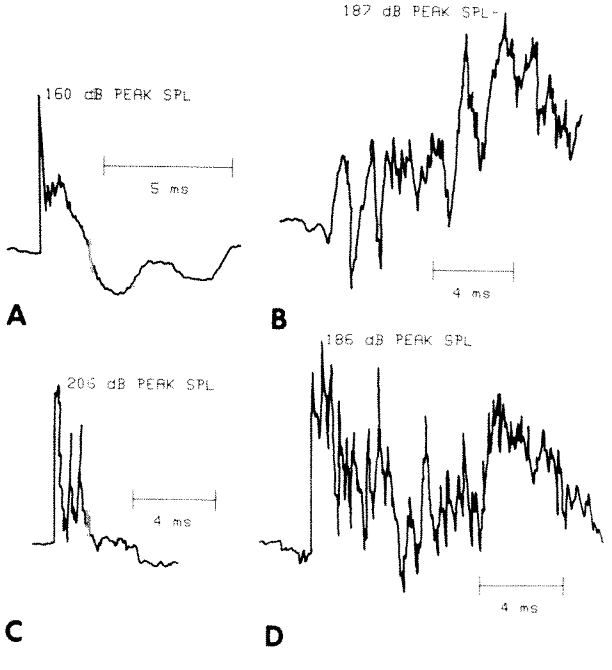

Fig 1. Pressure-time histories of impulses from A) chinchilla and B-D) pig/sheep exposures.

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TABLE 1. CLASSIFICATION OF TYMPANIC MEMBRANE PERFORATIONS AND MALLEUS FRACTURES IN SHEEP AND PHYSICAL CHARACTERISTICS OF IMPULSE*

Animal	*SPL (dB)*	*$I_{2.1}$ (kPa·ms)*	*I_{21} (kPa·ms)*
Group 1: small round perforation of pars tensa			
1237R	196	106	836
1243L	193	61	659
1240R	193	64	181
1232L	186	45	249
1249R	198	137	1,117
1243R	193	61	659
1197R	197	98	7,098
1197L	197	98	7,098
1240L	193	63	181
$\bar{x}$	194	81	2,009
SD	3.6	30	2,902
Group 2: kidney-shaped perforation of pars tensa			
1196L†	194	106	2,048
1165R	192	114	924
1162R†	178	17	532
1161L	190	63	878
1161R†	190	63	878
1351R†	208	295	1,946
1256R†	196	202	1,329
1237L	196	106	836
1165L†	192	114	924
1253L	204	210	1,607
$\bar{x}$	194	129	1,190
SD	8.2	83	516
Group 3: subtotal perforation of pars tensa			
1253R†	204	210	1,607
1250L	206	238	4,668
1250R†	206	238	4,668
1256L	196	202	1,329
$\bar{x}$	203	222	3,068
SD	5.0	19	1,851
Group 4: attic and pars tensa perforation			
1278L	201	226	1,164
1278R	201	226	1,164
1277R†	203	436	5,843
1277L†	203	436	5,843
1259L	204	222	4,349
1249L†	198	137	1,117
1350R†	195	125	2,407
$\bar{x}$	201	258	3,270
SD	3.0	128	2,039

R — right ear, L — left ear.

*Impulse taken over first 2.1 or 21 ms of waveform.

†Malleus fracture.

TABLE 2. CLASSIFICATION OF TYMPANIC MEMBRANE PARS TENSA PERFORATIONS AND MALLEUS FRACTURES IN PIG AND PHYSICAL CHARACTERISTICS OF IMPULSE*

Animal	*SPL (dB)*	*$I_{2.1}$ (kPa·ms)*	*I_{21} (kPa·ms)*
Group 1: inferior fusiform perforation			
1348R	209	194	6,845
1195L	184	28	812
1258L	206	239	5,565
$\bar{x}$	200	154	4,407
SD	13.7	111	3,179
Group 2: kidney-shaped perforation			
1258R†	206	239	5,565
1276R†	203	220	1,046
1349R†	197	224	2,036
1251R	202	193	1,066
1251L	202	193	1,066
1164R	184	26	624
1164L	184	26	624
1257R	205	199	1,823
1257L	205	199	1,823
1248R	197	157	1,232
1248L†	197	157	1,232
1255R	202	174	1,232
1255L†	202	174	1,232
1236R	194	57	523
1195R	184	28	703
1245R†	191	47	182
1245L†	191	47	182
1239R†	192	78	872
1239L†	192	78	872
1252R	206	342	3,612
1252L	206	342	3,612
$\bar{x}$	197	152	1,484
SD	7.6	97	1,308
Group 3: double inferior perforation			
1349L	197	224	2,036
Group 4: subtotal perforation			
1348L	209	194	6,845

R — right ear, L — left ear.

*Impulse taken over first 2.1 or 21 ms of waveform.

†Malleus fracture.

nuclear weapons testing. These studies are reviewed amply by Kokinakis and Rudolph.[4]

At the lower levels of exposure, ie, 150 to 160 dB, Eames et al,[5] using tympanometry to study middle ear function in chinchillas following exposures, found a variety of tympanometric functions during the early postexposure recovery period. Prior to perforation of the tympanic membrane, irregular tympanograms were identified with stress and probable rupture of the radial fibers, producing a floppy but not perforated membrane. A thorough histologic study of the middle ear and cochlea in chinchillas exposed to high levels of infrasound was presented by Lim et al.[6] Because of the strong low frequency biased spectrum of blast waves, the results of Lim et al may be of some interest. Damage ranged from a loss of localized patches of tympanic membrane epithelia to slitlike ruptures of the membrane. They also found bleeding of the tensor tympani muscle and hematoma in the lamina propria of the tympanic membrane. In some animals severe cochlear and saccular damage also was noted.

A number of clinical reports on blast trauma appear sporadically in the literature. These case studies are usually coincident with acute exposure to blast overpressures from explosions resulting from accidents in the civilian sector or following periods of armed conflict.[7-9] A brief historical review can be found in Keller.[10] In these clinical reports, most of which concern tympanic membrane damage and the associated hearing loss, details of the exposure variables can only be estimated.

There are far fewer reports on the histologic changes in the cochlea following blast wave exposure. The most recent studies by Hamernik et al[11-13]

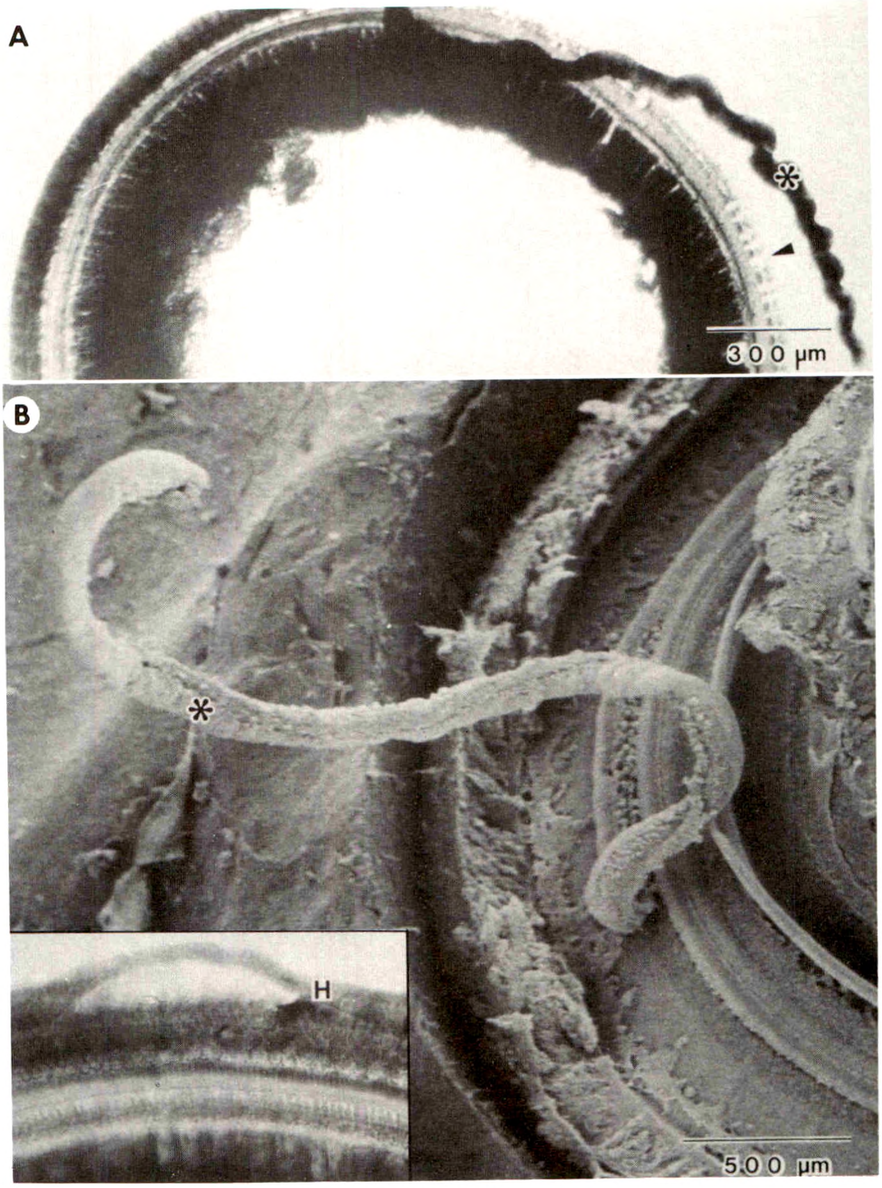

Fig 2. Views of organ of Corti in chinchilla. A) Low magnification surface preparation view of noise-induced separation of organ of Corti (*). Arrowhead — region of damage to sensory cells. B) Scanning electron micrograph of similar noise-induced fracture (*). Inset) Surface view of initial stages in dislocation of organ of Corti. In this specimen, fracture begins along Hensen-Deiters cell junction (H).

using the chinchilla as the experimental animal have shown clearly the extensive mechanical damage that can take place in the structure of the organ of Corti. However, only a very narrow range of waves was investigated. This paper will review some of the findings in the chinchilla and present additional information on the pig and sheep auditory responses to blast wave exposure.

METHODS

The information presented in this paper was obtained from several different blast wave studies using young mature chinchillas, pigs, and sheep of either sex. The chinchillas were exposed to "Friedlanderlike" waveforms generated with a shock tube that produced a peak SPL of 160 dB. The impulses were presented at a rate of 2/min for 50 minutes. The animals were killed painlessly immediately following exposure. Initial fixation was with 5% glutaraldehyde in veronal acetate buffer at pH 7.3 (630 mosm) for 24 hours followed by postfixation for 15 minutes in a glutaraldehyde/osmium mixture in a ratio of 5:2. The osmium was a 2% aqueous solution. The condition of the tympanic membrane was checked with an otoscope prior to killing. Animals were decapitated and their temporal bones carefully removed. The bulla was opened with no disturbance to the conductive system, and the bone was trimmed to allow artifact-free photography of the tympanic membrane. Complete details of the chinchilla studies can be found in Hamernik et al.[11,12] The descriptions of trauma in the chinchilla are primarily qualitative and are included only to illustrate the common mode of failure in the cochlea across several species of mammals exposed to blast waves.

The pigs and sheep were killed by lethal injection approximately 1 to 3 hours following exposure. The heads were sectioned along the midsagittal plane, and the temporal bones were removed quickly and

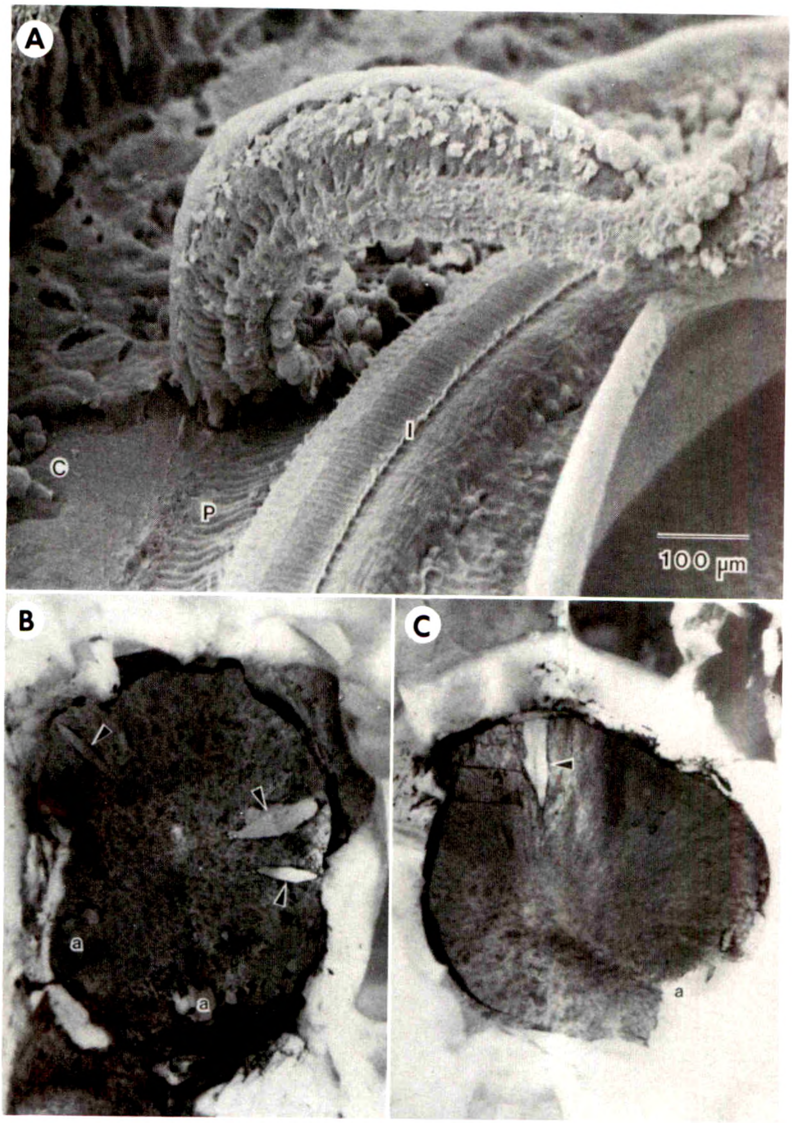

Fig 3. A) Higher magnification scanning electron micrograph of dislocated mass of organ of Corti. Note relatively intact line of inner hair cells (I) and outer pillar cell processes (P). Some Claudius cells (C) also have been dislodged. B,C) Two osmium-stained examples of ruptured chinchilla tympanic membrane viewed from external meatus. In chinchilla, ruptures (arrowheads) were invariably B) fusiform or C) triangular. a — artifact.

carefully. A small opening was made into the middle ear space to expose the cochlear windows, the ossicles, and the tympanic membrane. At this point, an initial cursory examination of the conductive system was made with a stereomicroscope to identify damage due to blast overpressure. The cochlea then was fixed via perilymphatic perfusion of 2.5% glutaraldehyde in veronal acetate buffer at pH 7.3 (605 mosm). Fixation took place within 15 minutes of death. The temporal bones then were stored in fixative in a refrigerator for up to 6 months. Cochlear dissections and a second, more detailed, evaluation of the tympanic membranes were undertaken after carefully separating the incudostapedial joint and separating the otic capsule from the temporal bone. The cochleas were postfixed in 1% osmium tetroxide in veronal acetate buffer for 15 minutes. The cochleas that were to be mounted as surface preparations then were washed and dehydrated to 70% ethyl alcohol, and the temporal bones were drilled and picked free of bone in order to expose the membranous labyrinth. The complete organ of Corti was dissected free of its bony attachments and mounted in glycerin as a conventional surface preparation.[14] As a gross measure of trauma, the total number of inner and outer sensory cells missing in each cochlea was established by use of a Zeiss-Nomarski light microscope at a magnification of 500x. The cochleas that were viewed under the scanning electron microscope were submitted to a similar initial fixation protocol, but were dehydrated to 100% ethyl alcohol following a partial dissection that exposed the membranous labyrinth. The temporal bones then were critical point dried with liquid carbon dioxide, and gold-palladium was sputtered onto each specimen. The specimens were viewed with a JEOL JSM-35 scanning electron microscope operating at 15 keV.

Before we present any of the results from these studies, the following points should be noted. Since the animals were killed very soon after exposure, the extent of the sensory cell loss is, at best, only an approximation. In fact, the sensory cell losses ac-

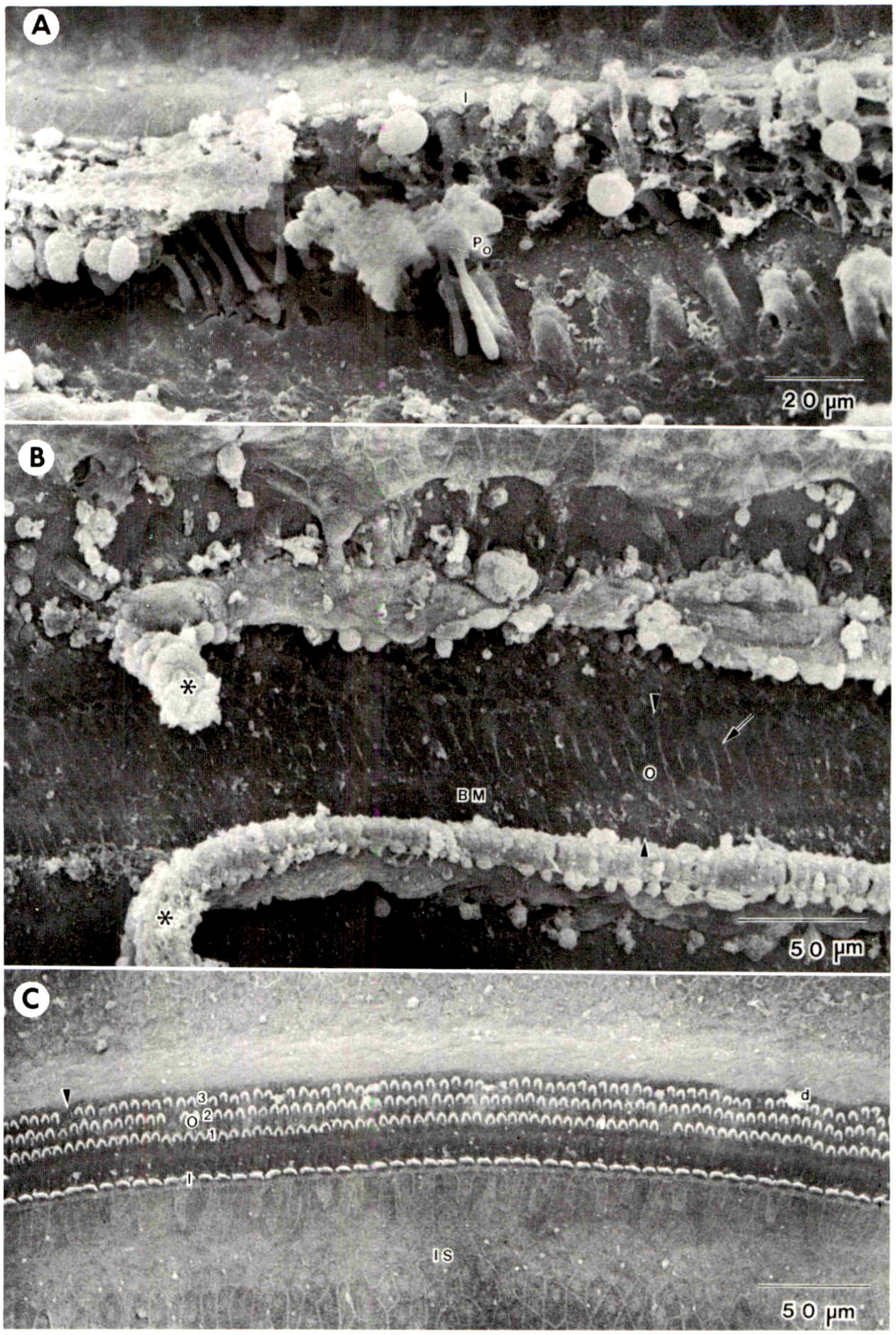

Fig 4. Scanning electron micrographs from three regions of pig cochlea 1183L. A,B) Basal portion. Organ of Corti is severely destroyed. In A, some inner hair cells (I) still can be seen and outer pillar cell processes (Po) are recognizable. In B, loose pieces of organ of Corti (*) can be identified. These fragments are similar to those seen in surface preparation micrograph of Fig 5B and consist mostly of supporting cells. Basilar membrane (BM) retains imprints (arrow) marking former sites of attachment of supporting pillar cells or Deiters' cells. Region marked by O and arrowheads is devoid of all sensory cells. C) Apical portion. Most of inner (I) and outer (O) hair cells are present, and organ of Corti generally appears normal. Some outer hair cells are missing (arrowhead) and particles of debris (d) are common. IS — inner sulcus, 1, 2, 3 — rows of outer hair cells.

tually represent a lower limit to the sensory cell losses that would eventually develop if each animal had been allowed a sufficient recovery period for the lesion to stabilize through the formation of scar tissue. Following a severe trauma, sensory cell losses in the cochlea continue to increase over a period of several weeks, especially if the integrity of the reticular lamina is compromised severely.[14-16] Also, in most of the cochleas examined, there are many cells that are present, but are damaged severely (eg, missing cilia, badly swollen, lacking supporting elements) and may never function normally, but are counted as present. The second point is that the investigator (G.A.T.) who removed the temporal bones was experienced in their removal from pigs and sheep. A large number of temporal bones were removed from freshly killed normal animals in order to develop a technique that consistently produced no visible artifacts in the middle ear. Thus we were reasonably confident that the middle ear defects that were first visualized and graded through a small hole into the middle ear cavity were the result of the noise exposure. The removal of the otic capsule from the temporal bone in the pigs and sheep was more difficult, and some temporal bones were rejected from the second, more detailed, description of the tympanic membrane because of preparation artifacts.

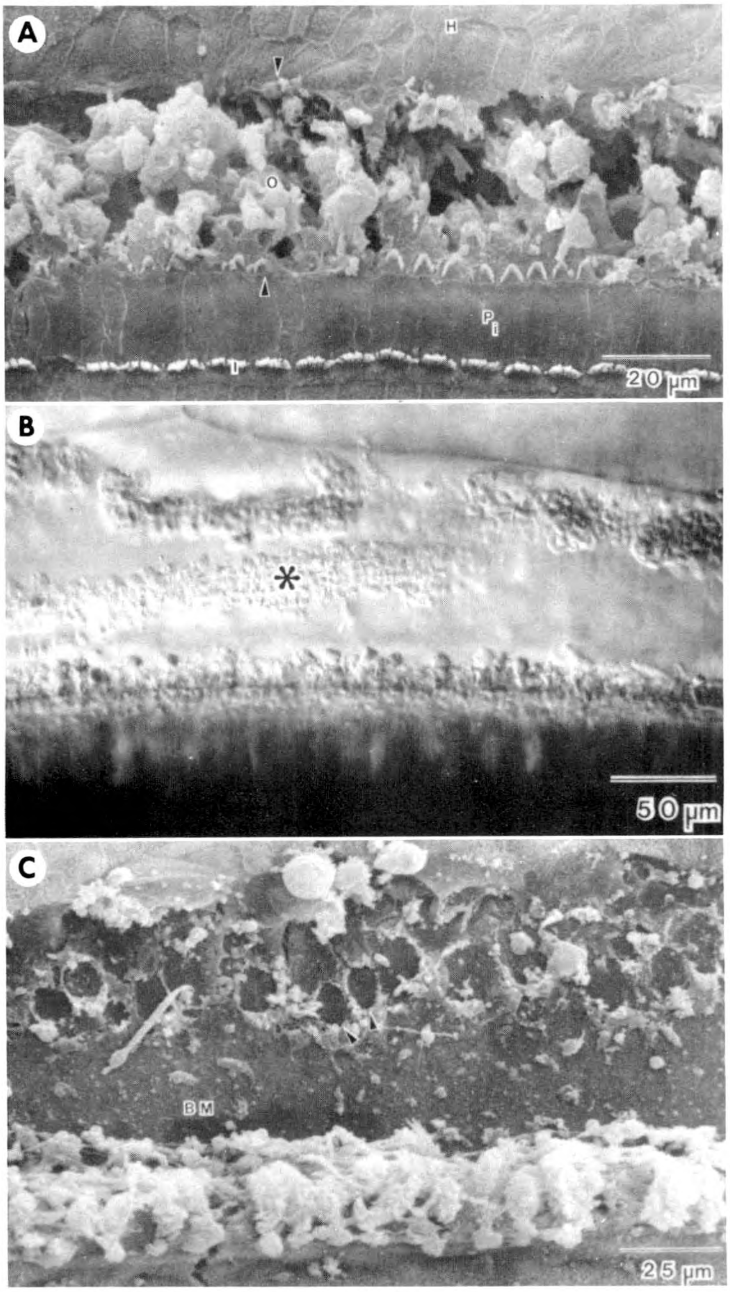

Fig 5. A) Region of organ of Corti from pig cochlea 1348R, apicalward of specimen shown in C. Most inner hair cells (I) are present and relatively normal in appearance. Some outer hair cells are present and have relatively normal-appearing complement of cilia. However, reticular lamina still is damaged severely and supporting cells are disrupted. H — Hensen's cells, Pi — inner pillar cells, O and arrowheads — region of outer hair cells. B,C) Regions of organ of Corti from pig cochleas 1195L and 1348R, respectively, that illustrate focal point of lesion. C) Complete absence of all sensory elements on basilar membrane (BM). Imprints of supporting cell attachments (arrowheads) are prominent and debris is plentiful. B) Similar surface preparation view in which all sensory cells are either missing or organ of Corti (*) is torn away from basilar membrane and is floating in scala media loosely attached at few points.

One hundred eight temporal bones were examined from 26 pigs and 28 sheep; one sheep temporal bone was rejected because of otitis media. Surface preparation histology was performed on 15 cochleas of each species, and five cochleas of each species were prepared for scanning electron microscopy.

RESULTS AND DISCUSSION

Stimulus. Figure 1A illustrates the shock tube waveform to which the chinchillas were exposed. The wave was repeatable and the peak intensity could be controlled to within ±1 dB. The waveforms to which the pigs and sheep were exposed were extremely variable as a result of the field exposure conditions. A selection of pressure/time traces is presented in Fig 1B-D. The overall mean peak SPL that the sheep ($n = 55$ ears) were exposed to was 195 dB, with a standard deviation of 7 dB and a range of 178 to 208 dB. For the pigs ($n = 52$ ears), the peak SPL was also 195 dB, with a standard deviation of 7 dB and a range of 184 to 209 dB. Thus on the average the pigs and the sheep were exposed to similar intensity waves. An additional indication of the differences between the wave pressure/time profiles can be obtained by computing the impulse per unit area (I) of the wave, ie,

$$I = \int_{o}^{t} P(t)dt \qquad (\text{kPa}\cdot\text{ms})$$

where $P(t)$ = time-varying pressure.

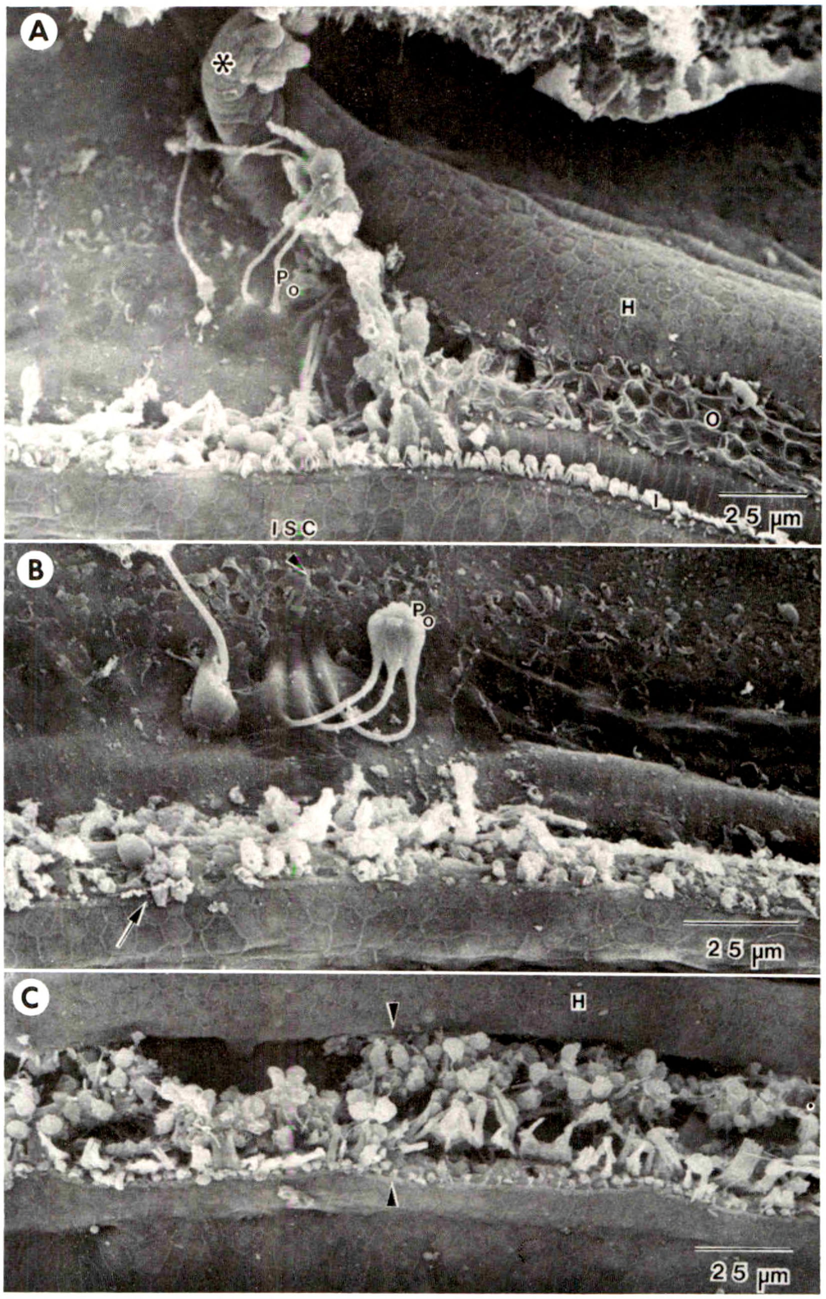

Fig 6. A) Scanning electron micrograph from sheep cochlea 1158L illustrating tearing away of organ of Corti from its basilar membrane attachments. This is basal edge of extensive lesion. Mass of Hensen's cells (H) is clearly seen to form independent strip of tissue (*) as it is peeled back toward base. Attached to it are remains of other supporting cells. Processes of outer pillar cells (Po) are visible. Inner hair cells (I) are present in variety of conditions. O — outer hair cells, ISC — inner sulcus cells. B) Farther apicalward of lesion in A, very few cells of organ of Corti are left on basilar membrane. Some isolated outer pillar cells (Po) are left; some remnants of inner hair cell supporting elements and isolated inner hair cell (arrow) can be discerned. Imprints of attachments of other supporting cells are visible (arrowhead). C) In central region of lesion in specimen 1162L, mass of Hensen's cells (H) did not separate from basilar membrane, but section of organ of Corti containing sensory cells (region between arrowheads) still is damaged severely and little trace of reticular lamina remains. Lesion leaves open rift between inner sulcus and Hensen's cells that is filled with degenerating sensory and supporting cells. Most inner hair cells are missing or damaged severely.

Two different time windows of 2.1 ms and 21 ms were used for each wave, and values for $I_{2.1}$ and I_{21} were obtained. Some indication of the variability in these values can be obtained from Tables 1 and 2. Such an integration should provide a means of classifying the widely differing waveforms, and perhaps an index to their relative potential for causing acoustic trauma.

Cochlear Changes. The most profound damage to the organ of Corti in all three species studied was a fracture of the reticular lamina and a dislocation of a large portion of the organ of Corti from the basilar membrane. Figure 2 illustrates surface preparation and scanning electron micrographs of the chinchilla organ of Corti. In Fig 2A the dislocated organ of Corti can be seen clearly. A similar scanning electron microscopic view is presented in Fig 2B. Because of the intersubject variability, some cochleas showed only the initial stages of the fracture (inset). Figure 3A illustrates the fracture zone at a higher resolution. Considering the extreme damage, it is surprising that the inner hair cells appear intact and relatively normal. A similar fracture in the sheep and the pig cochlea is shown and described in Figs 4 through 6. The extent of the fracture as well as the total number of sensory cells destroyed is quite variable. This variability may reflect individual susceptibility or a variation in the stimulus as to the position of the animal's head. Total cell counts for the 15 pig and 15 sheep cochleas that were dissected are presented in Table 3. Variations in cell counts could not be correlated with the

TABLE 3. SUMMARY OF TOTAL NUMBER OF SENSORY CELLS LOST, MIDDLE EAR FINDINGS, AND EXPOSURE LEVELS FOR 30 COCHLEAS SUBMITTED TO SURFACE PREPARATION HISTOLOGY

Animal	*No. Inner Hair Cells Lost*	*No. Outer Hair Cells Lost*	*Middle Ear Code**	*Peak SPL (dB)*
Sheep				
1351R	1,163	6,363	4	208
1197R	781	5,232	4	197
1182R	892	6,471	1	197
1180R	646	5,883	1	192
1165R	443	5,437	4	192
1158R	235	5,275	4	182
1256R	582	4,994	4	196
1196R	145	2,918	2	194
1277R	703	3,922	4	203
1249R	175	2,155	2	198
1244R	469	2,006	2	190
1162R	21	1,823	3	178
1129R	33	861	N/A	176
1250R	5	430	4	206
1259R†	21†	174†	—	—
$\bar{x}$	450	3,841		194
SD	362	2,093		9.6
Pigs				
1348R	560	4,725	3	209
1257R	48	3,695	3, 5	205
1257L	52	2,909	3, 5	205
1349L	403	2,951	1	197
1258R	31	3,113	4	206
1242R	13	2,967	1	200
1195R	43	3,749	3	184
1166R	14	3,127	1	197
1164R	43	3,717	4	184
1130R	504	3,605	N/A	171
1131R	8	1,688	N/A	180
1164L	20	881	3	184
1349R	8	398	4	197
1248R	9	613	4	197
1183R	9	595	1	185
$\bar{x}$	118	2,580		193
SD	195	1,386		11.3

R — right ear, L — left ear, N/A — not assessed because ear damaged in preparation.

*1 — normal, 2 — small perforation, 3 — large perforation, 4 — fracture of handle of malleus and perforation of tympanic membrane, 5 — disarticulation of stapes from oval window.

†Rejected because of preexisting otitis media.

condition of the middle ear, nor with physical measures of the stimulus such as peak SPL or $I_{2.1}$ and I_{21}. Other, more subtle indications of mechanically induced damage are shown in Figs 7 and 8. In pigs, sheep, and chinchillas the cilia on both inner and outer hair cells, especially the tallest cilia, are subject to fracture or bending, usually about their point of insertion into the cuticular plate.

Although the average measures for the total sensory cells lost in each species (Table 3) are only a crude indicator of the species susceptibility, especially considering the great variability in exposure waveforms, the mean data may be instructive. The total inner hair cell and outer hair cell losses given in Table 3 show, on a percentage basis, 20.6% of the inner hair cells and 47.5% of the outer hair cells to be lost in the sheep and 3.3% of the inner hair cells and 17.7% of the outer hair cells to be lost in the pig. The mean peak SPL for the two groups whose cochleas were dissected is quite similar: 194 dB for the sheep and 193 dB for the pigs. The differences between the mean percentages of sensory cell loss between the two species was submitted to a *t* test. The sheep in this sample suffered significantly greater hair cell loss than did the pigs (inner hair cells: $t = 3.81$, $p < .001$; outer hair cells: $t = 4.17$, $p < .001$). Thus, on the basis of this limited sample, the sheep appear to be more susceptible to acoustic trauma than the pigs.

Middle Ear. The first evaluations of the middle ear prior to removal of the otic capsule from the temporal bone produced the following information. In the sheep, of a sample of 55 temporal bones, nine middle ears appeared normal (16%). The mean exposure for these nine ears was 191 dB peak SPL (SD = 4.3 dB). Two tympanic membranes showed hemorrhagic infiltration of the lamina propria, without any membrane perforation. Forty-four middle ears (80%) showed rupture of the tympanic membrane, with 29% of these showing a fracture of the malleus handle. These 44 ears were exposed to a mean peak SPL of 196 dB (SD = 6.8 dB). A *t* test indicated that the above two mean SPLs were statistically different ($p < .05$). In the pigs, of a sample of 52 temporal bones, 25 middle ears appeared normal (48%). The mean exposure for these 25 ears was 193 dB peak SPL (SD = 4.6 dB). Twenty-seven middle ears (52%) showed rupture of the tympanic membrane, of which 25% also had a fracture of the handle of the malleus. These 27 ears were exposed to a mean peak SPL of 197 dB (SD = 8.5 dB). A *t* test indicated that the mean peak SPLs for the two groups of pigs (ie, those with perforations and those without) were statistically different ($p < .05$).

The second evaluation of the condition of the tympanic membrane took place after removal of the otic capsule. This allowed an unobstructed view of the entire tympanic membrane and malleus-incus complex. Of the 44 sheep temporal bones that showed some membrane rupture, we were able to remove the otic capsule from 30 without introducing any artifacts. Also, 25 of the 27 pig temporal bones with membrane perforations could be prepared in similar fashion. The acute alterations in these pig and sheep middle ears that are clearly related to the acoustic trauma are listed below and in Tables 1 and 2.

Hemorrhagic infiltration of the lamina propria of the tympanic membrane generally was seen as a ring around the periphery of the pars tensa (Fig 9A) or immediately below the anterior (Fig 9A) and posterior malleal folds (Fig 10B). It was seen less frequently along the sides of the handle of the malleus (Fig 10B,C,F). Hemorrhagic infiltration was seen in all the ears of both pigs and sheep that

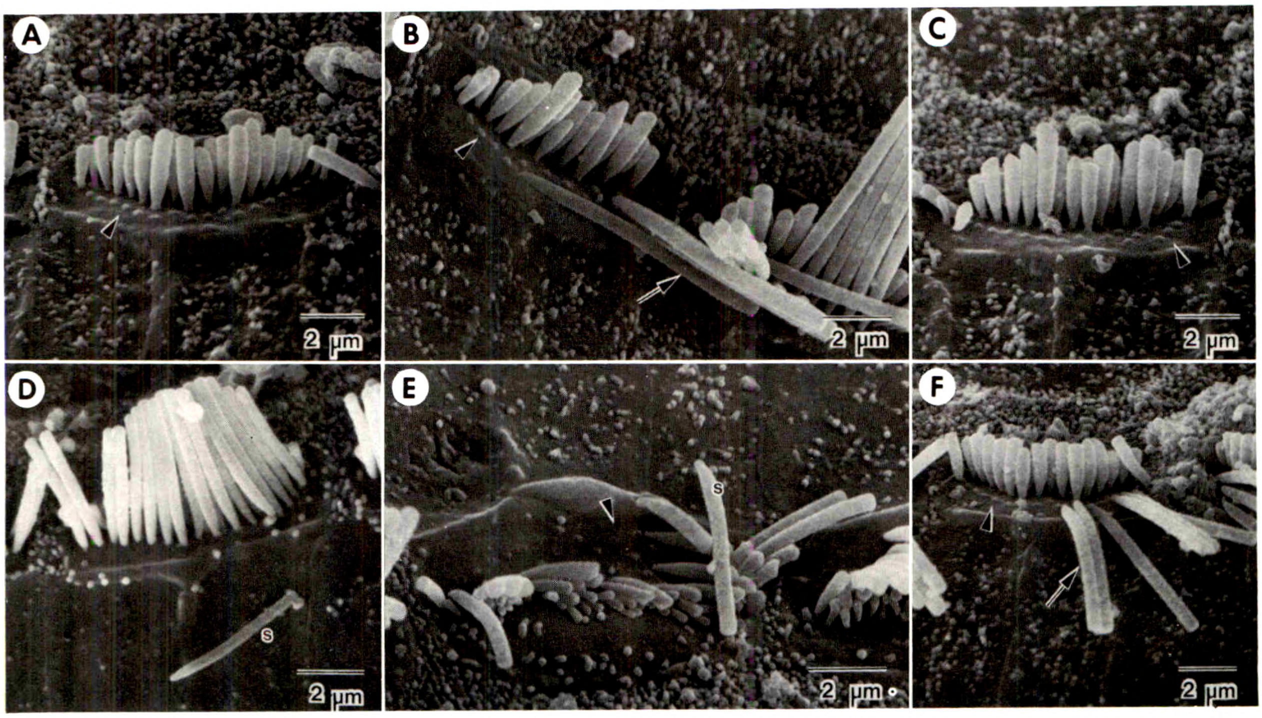

Fig 7. In areas of organ of Corti in which sensory cell populations were near normal, cilia often were disturbed severely. A-F) Scanning electron micrographs showing examples of stereocilia changes in pig cochlea that were frequently seen on inner hair cells. Tallest cilia have been broken off (arrowheads) and stumps of cilia are seen on surface of cuticular plate. Many cilia are bent over at their points of insertion into cuticular plate (arrows) in B and F and in some examples broken cilia fragments (s) in D and E can be found lying near inner hair cells.

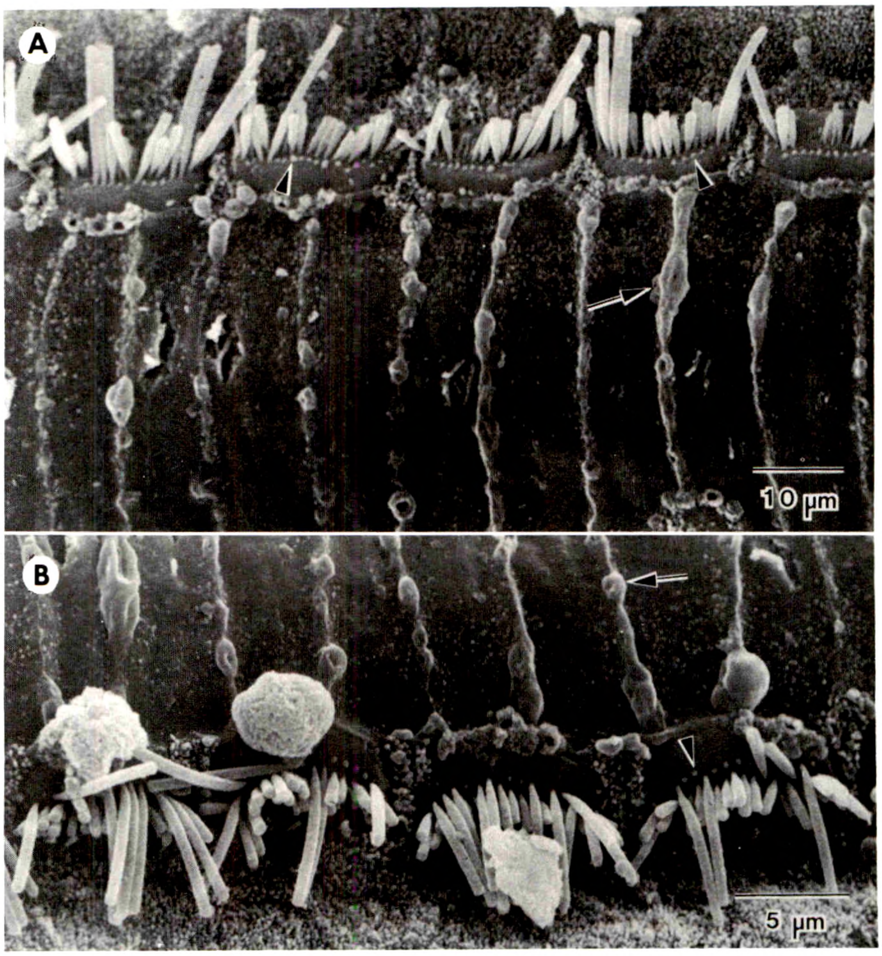

Fig 8. On basal end of primary lesion in sheep cochlea 1244L in regions of organ of Corti in which outer hair cells are missing or damaged, extensive number of inner hair cells can be found (as in pig cochlea shown in Fig 7) with tallest row of cilia broken off (arrowheads). Unusual evaginations (arrows) at junctions of inner pillar cells were seen throughout this cochlea.

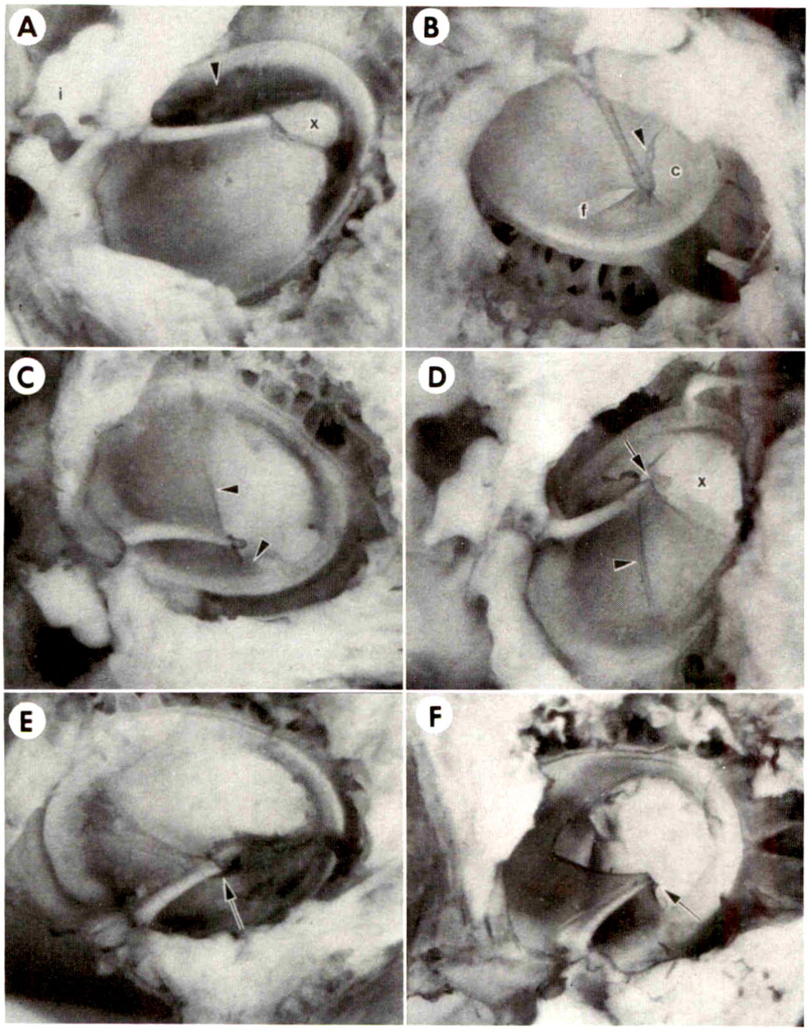

Fig 9. Examples of perforations seen in pig tympanic membrane (pars tensa) viewed from within middle ear looking outward. A) Small triangular inferior perforation (x) with hemorrhagic infiltration of lamina propria around periphery and below anterior malleal fold (arrowhead). Incus (i) is seen in place, well articulated with head of malleus and covering pars flaccida. B) Only case of double perforation, fusiform (f) in posterior-inferior quadrant and circular (c) in anterior-inferior quadrant. Note everted margins (arrowhead) of circular perforation. C) Large perforation of inferior part of pars tensa. Superior margins (arrowheads) of perforation follow radial fibers of lamina propria. D) Triangular inferior perforation (x) and posterior linear fold (arrowhead) are seen. Small fracture (arrow) of tip of handle is also visible. E,F) Two typical kidney-shaped perforations associated with fracture (arrows) of distal third of handle. Margins of perforations follow parabolic and radial fibers of lamina propria.

showed tympanic membrane perforations and in two of the sheep that had no perforations or other visible signs of trauma.

In the sheep the perforation of the tympanic membrane varied from small, "round" (1 to 3 mm) holes generally located in the anterior and posterior quadrants of the pars tensa just below the anterior and posterior malleal folds to large, uniformly sized holes that were kidney shaped and centrally located in the pars tensa (Fig 10C-E). A few of the subtotal perforations left only remnants of the tympanic membrane. We never found fusiform perforations, as were sometimes seen in the pig and most often in the chinchilla (Fig 3B,C). Some sheep showed a combination of two perforations (ie, kidney-shaped and round, or two round) of the pars tensa. Perforations of the pars flaccida were seen in several animals and were always round in shape and quite large (>3 mm). The area of the pars flaccida is much larger in the sheep than in the human, having a surface area approximately the same as that of the pars tensa (Fig 10A,D,F). Despite its large area, perforations of the pars flaccida were always seen in combination with the most severe lesions of the pars tensa.

In the pigs the perforations were most often of a kidney shape and of variable size, usually not extending to the tympanic annulus. A few of the pigs showed triangular or fusiform perforations in the inferior part of the pars tensa (Fig 9A,B). Unlike in the sheep, the margins of the perforations in the pig follow the radial or the parabolic fibers of the lamina propria (Fig 9C,F), much like the perforations usually found in traumatic perforations of the human tympanic membrane. No perforations of the pars flaccida were seen in the pig.

Of the 30 tympanic membrane ruptures in the sheep listed in Table 1, 13 temporal bones showed a fracture of the handle of the malleus. The point of fracture was variable, occurring either at the neck or in the first third, the middle third (Fig 10E), or the last (most distal) third of the handle with about equal frequency. The fractures differed in the pig, in that the fracture occurred usually in the distal third of the handle (Fig 9D-F). In the 26 pig temporal bones examined, there were nine fractures.

Correlations With Traumatizing Stimulus. We attempted to develop statistical correlations between different severities or categories of perfora-

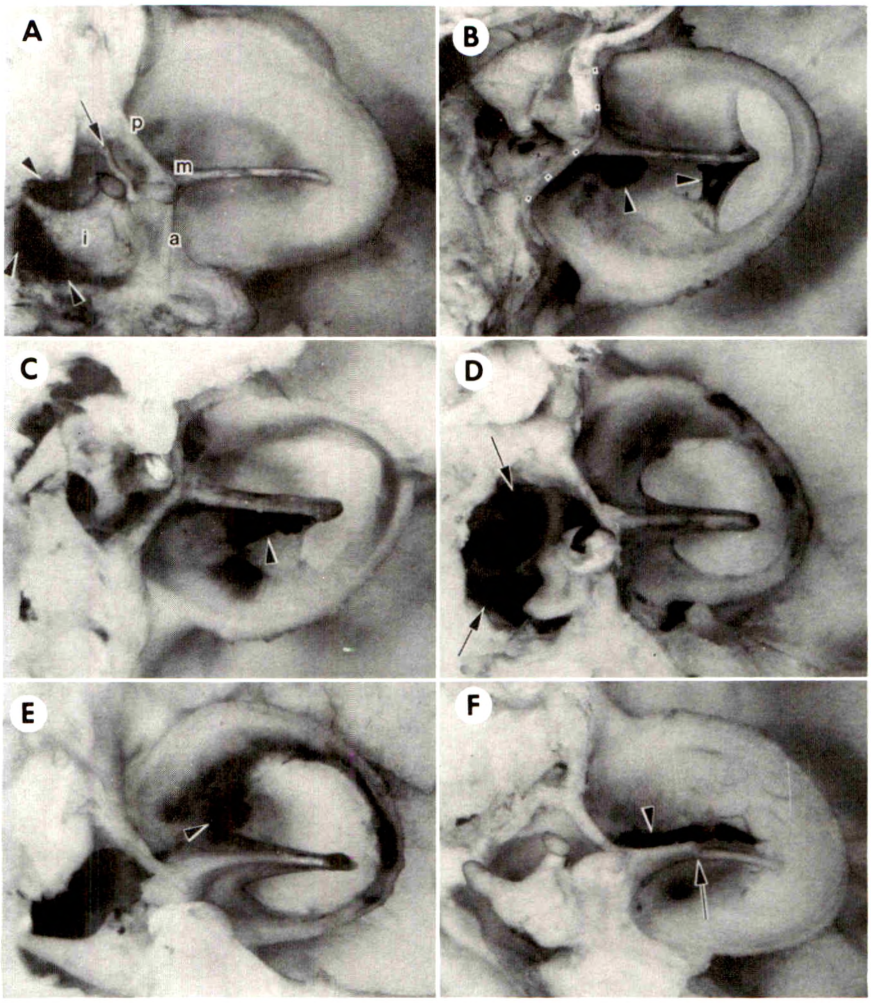

Fig 10. Examples of perforations seen in sheep tympanic membrane (pars tensa) viewed from within middle ear looking outward. A) Normal aspect of tympanic membrane and ossicles (incus [i] and malleus [m]) with anterior (a) and posterior (p) malleal folds. Portion of pars flaccida seen in this view is indicated by arrowheads. Attachment of tensor tympani to neck of malleus is visible (arrow). B) Small kidney-shaped perforation with hemorrhagic infiltration (arrowheads) below posterior malleal fold and along posterior side of handle. Corda tympani clearly is visible (....). C-E) Three large kidney-shaped perforations with hemorrhagic infiltrations (arrowheads in C and E). In D, incus was removed in order to show more clearly pars flaccida with hemorrhagic clots (arrows). F) Fracture of middle third of handle of malleus with clot (arrowhead). Dislocation of fragment is seen clearly (arrow).

tion as listed in Tables 1 and 2, and the mean peak SPL of the blast wave or with the mean impulse (I) of the waveform.

As indicated in Table 1, the perforations in sheep were categorized according to size and location into four groups, with the mean exposure parameters as indicated. The only good correlations were made with peak SPL and showed that perforation groups 1 and 2 were similar and that groups 4 and 5 were similar but different from groups 1 and 2. The impulses $I_{2.1}$ and I_{21}, because of their large variability, were not good predictors of damage for our limited sample.

Almost all of the tympanic membrane perforations in the pigs were kidney shaped, and all of the malleus fractures were associated with these kidney-shaped perforations. Because of the small sample size of the other groups of perforations, correlations with wave parameters would not yield meaningful results.

Thus, it would appear that the sheep are somewhat more susceptible to middle ear failure, since the first signs of trauma, ie, small circular perforations or kidney-shaped perforations of the tympanic membrane, begin to occur at mean peak SPLs of around 194 dB, while consistent perforations in the pig occur at mean peak SPLs of around 197 dB. In neither species could the presence or absence of a fracture be correlated with any of the exposure variables.

One hundred impulses (2/min) at an exposure intensity of 160 dB produced one to several radial slitlike tympanic membrane perforations (fusiform) in approximately half the chinchilla temporal bones examined (n = 52 ears). These perforations (Fig 3B, C) always were associated with hemorrhagic infiltration of the lamina propria. Unlike in the pig and the sheep, many of the tympanic membranes in the chinchilla that were not perforated showed hemorrhagic infiltration of the lamina propria.

CONCLUSIONS

1. On the basis of these limited data, the chinchilla would appear to be most susceptible to middle ear blast trauma, followed by the sheep and then the pig.
2. There is a similarity across all three species in the manner in which the organ of Corti is mechani-

cally damaged.

3. For similar conditions of exposure, the sheep is more susceptible to cochlear trauma than the pig.

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PHYSICAL CORRELATES OF EARDRUM RUPTURE

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Eardrum (tympanic membrane) rupture in humans and animals in relation to various blast pressure-time patterns was reviewed. There were few systematic studies on eardrum rupture as a consequence of blast overpressure. Most reports did not describe the area of the eardrum destroyed. The peak overpressures required to produce a 50% incidence of eardrum rupture (P50) were summarized. Most of the animal data pertained to dogs. The highest P50 for dogs, 296 kPa, was associated with smooth-rising overpressure. For complex wave patterns occurring inside open shelters subjected to nuclear blasts, the P50 was 205 kPa. For fast-rising blasts in a shock tube it was 78 kPa, and 105 kPa for statically applied pressures. The duration of the overpressure was not a factor unless it was very short. The influence of the orientation of the head to the oncoming blast was demonstrated. An ear facing the blast may receive reflected overpressures several times that for one side-on to the blast. An ear on the downstream side of the head was exposed to about the same overpressure as the side-on ear. A P50 for humans of 100 kPa and a threshold of 35 kPa has been used widely in blast criteria. A recent study suggests a threshold (P1) of about 20 kPa, and gives the overpressures required to produce minor, moderate, and major eardrum ruptures. These data were presented in the form of curves showing the overpressures as a function of duration required to inflict a P1 and a P50 of eardrum rupture of the three levels of severity.

KEY WORDS — airblast on ears, barotrauma, blast criteria, blast effects, blast pathology, eardrum rupture.

INTRODUCTION

The wide variability in human eardrum (tympanic membrane) response to blast is well known. It has been suggested many times that the variation is due to the physical geometric features of the ear including the size and shape of the pinna; the length and diameter of the external auditory meatus, as well as the amount of cerumen and squamous material in the canal; past and present pathologic conditions; and age. In addition, White et al[1] have suggested that the eardrum may bottom out against the inner walls of the middle ear and in those instances withstand rather high overpressures. White et al also pointed out that the air in the middle ear may act as a spring, providing increasing resistance to displacement as the drum moves inward. Some recent experiments have borne out this hypothesis. Openings have been made into the middle ear that lessened the resistance of the drum to inward movement. The purpose of this presentation is

1. To review the data on the response of animal and human eardrums to several pressure-time patterns: those that are fast-rising, as generated by explosives and in shock tubes; smooth-rising ones, produced by a modified shock tube or apparatus that applies the overpressure statically to the ear canal; and complex patterns, occurring inside structures.
2. To illustrate the pressure loading at the eardrum with respect to how the head is oriented to the blast.
3. To discuss briefly a blast-casualty criterion based on a severe form of ear injury.

ANIMAL EARDRUM RESPONSE

Tables 1[1-5] and 2[2,3] summarize the peak overpressures required for a 50% incidence of eardrum rupture (P50) among the various animal species. The bulk of the information is from tests in shock tubes that produced sharp-rising waveforms and from animals exposed to complex waves in open shelters in the environment of nuclear detonations at the Nevada Test Site. The least amount of data is from subjects exposed to blast in the open who receive a peaked blast wave. Examples of fast-rising, smooth-rising, and complex pressure waves are illustrated in Fig 1.

Overpressure values from the shock tube studies reported by White et al[1] and Hirsch[2] were in terms of the reflected pressures, because the animals were mounted on a reflecting surface normal to the incident shock. For complex waves, the peak pressure was either in the reflected shocks or in the smooth-rising fill phase — whichever was the highest. Data reported by Blake et al[3] were assumed to be in terms

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REPRINTS — Donald R. Richmond, PhD, EG&G Mason Research Institute, Western Operations, PO Box 9024, Albuquerque, NM 87119.

TABLE 1. PEAK OVERPRESSURES REQUIRED FOR FIFTY PERCENT INCIDENCE OF EARDRUM RUPTURE IN LARGE ANIMALS

Species	*Reference*	*Peak Overpressure in Kilopascals (psi)*	*Waveform*
Dog	White et al[1]	78 (11.3)	Fast-rising, reflected shock (shock tube)
	White et al[1]	205 (29.8)	Complex
	Richmond & Kilgore[5]	296 (43.0)	Smooth-rising
	Zalewski[4]	103 (15.0)	Static
Monkey	Hirsch[2]	172 (25.0)	Fast-rising, reflected shock (shock tube)
	Blake et al[3]	138-172 (20-25)	Fast-rising, incident shock (shock tube)
Sheep	Richmond, unpublished observations	165 (24.0)	Fast-rising reflected shock (shock tube)
	Richmond, unpublished observations	>4,000 (>600)	Fast-rising, incident shock (0.45-kg charge, open), <0.5 ms duration
Goat	Hirsch[2]	59 (8.5)	Fast-rising, reflected shock (shock tube)
	White et al[1]	69 (10.0)	Fast-rising, incident shock (0.5-kiloton charge)

of the incident shock, because the shock tube was open-ended. The incident shock pressures also were applied to animals exposed to explosions in the open as reported by White et al[1] and Richmond (unpublished observations). The P50 for dog's eardrum rupture from fast-rising blast waves, 78 kPa (11.3 psi), was about the same as that for pressures statically applied (103 kPa [15 psi]).[4] Much higher P50 values were obtained with complex blast waves (205 kPa [29.8 psi]) and smooth-rising waves (296 kPa [43 psi]).[5] The smooth-rising waves had rise times (time to peak pressure) of 15, 30, 90, and 200 to 400 ms. There was little, if any, difference in the P50 for monkey eardrums, whether the pressure was fast-rising with incident shock waves of 138 kPa (20 psi) to 172 kPa (25 psi) or fast-rising with reflected shock waves of 172 kPa (25 psi). Among the large animals the P50 for fast-rising pressures was lowest for goats (59 kPa [8.5 psi] and 69 kPa [10 psi]). That the duration of wave can be important is demonstrated by the P50 values for sheep. For fast-rising overpressures of several hundred milliseconds' duration, the P50 was on the order of 165 kPa (24 psi); at durations of less than 0.5 ms, over 40 bar (>600 psi) was necessary.

As seen in Table 2,[2,3] the P50 for rabbits and guinea pigs subjected to complex waves was about four times higher than those obtained with fast-rising pressures in a shock tube.

In connection with repeated blasts, it can be seen in Table 2 that the P50 for rat eardrums dropped from 39 kPa (5.6 psi) for one blast exposure to 19 kPa (2.2 psi) for 20 blasts of exposure.[4] The relationship between the number of blasts, the incidence, and especially the severity of ear injuries needs defining.

Unfortunately, most of the reports on eardrum response to blast do not list the area of the tympanum destroyed. In evaluating the consequences of ear injury, the severity of the injury has not been taken into account. Figure 2 shows photographs of canine eardrums taken from the middle ear side. These lesions range from a small perforation and less than 50% of the tympanic membrane destroyed, to over 50% destroyed with hemorrhage, and to the drum completely gone with the malleus fractured. The extent of conductive hearing loss and discomfort to the individual undoubtedly depends upon severity of the ear injury.

HUMAN EARDRUM RESPONSE

One of the few studies on the response of human ears to pressure was that of Zalewski in 1906.[4] He used fresh preparations from cadavers less than 24 hours after death. Zalewski developed an apparatus to raise the pressure gradually (statically) in the ear canal. The shape of the pressure pulse was not measured. He could hear a crack when the eardrum ruptured. There were 232 experiments with ears from humans of different sexes, ages, and physiologic states.

TABLE 2. PEAK OVERPRESSURES REQUIRED FOR FIFTY PERCENT INCIDENCE OF EARDRUM RUPTURE IN RODENTS

Species	*Reference*	*Peak Overpressure in Kilopascals (psi)*	*Waveform*
Rabbit	Hirsch[2]	64 (9.3)	Complex
	Blake et al[3]	15 (2.2)	Fast-rising, incident shock (shock tube)
Guinea pig	Hirsch[2]	51 (7.4)	Complex
	Blake et al[3]	15 (2.2)	Fast-rising, incident shock (shock tube)
Rat	Richmond, unpublished observations	39 (5.6)	Fast-rising, incident shock, (0.45-kg charge, open, one blast)
	Richmond, unpublished observations	19 (2.8)	20 blasts

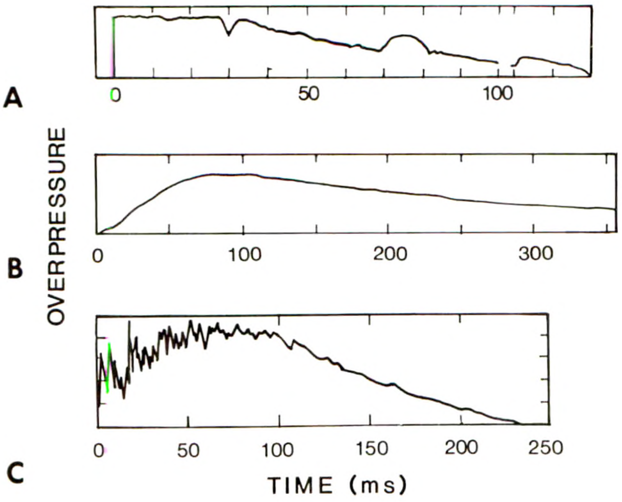


Fig 1. Pressure-time patterns. A) Fast-rising. B) Smooth-rising. C) Complex.

Zalewski found that for normal human eardrums the minimal and maximal pressures for rupture were 37 kPa (5.4 psi) and 298 kPa (43 psi), respectively. A mean value was 158 kPa (23 psi) (Table 3[2-4,6]). There was not a difference between normal eardrums from males and females or right and left. With normal eardrums, 66% failed at pressures between 1 and 2 atm; 11%, under 1 atm; and 23%, over 2 atm.

Zalewski reported that the resistance of the tympanic membrane to pressure is reduced with aging, scarring, thinning of the membrane, and inflammation in the middle ear or tympanic membrane. Development of connective tissue causes an increase in resistance. The lowest pressure at which a normal eardrum failed was 37 kPa (5.4 psi); for a scarred or inflamed one, it was about 6.8 to 14 kPa (1 to 2 psi).

Zalewski demonstrated that the ossicles provide some support to the tympanic membrane. In a sample of 52 ears, the incus and stapes were removed from the middle ear and the resistance of the eardrum was found to decrease on the average of 16 kPa (2.4 psi).

Blake et al[3] conducted experiments in a shock tube on 11 cadavers less than 24 hours after death. It was suggested that the 50% point for rupture was about 1 atm (100 kPa) (Table 3[2-4,6]). Details of the methods were not given; it may be assumed that the overpressures were sharp-rising and of fairly long duration (tens of milliseconds).

Observations also were made in air raid casualties by Blake et al.[3] The indications were that the pressure at which the human eardrum could be expected to rupture in 50% of the cases was on the order of 345 kPa (50 psi). There were a number of instances in which eardrums ruptured at 14 to 28 kPa (2 to 4 psi). A few records were available about the immediate symptoms associated with blast damage to the drum, middle ear, and inner ear. It was stated that blast damage to the ear often was associated with immediate pain and impairment of function. It occasionally occurred without causing any inconvenience and without the victim's being aware of what had happened.

In a review of the effects of overpressure on the ear, Hirsch[2] compiled a curve relating percent eardrum rupture in the human as a function of peak pressure (Fig 3[2]). This much-used curve was based

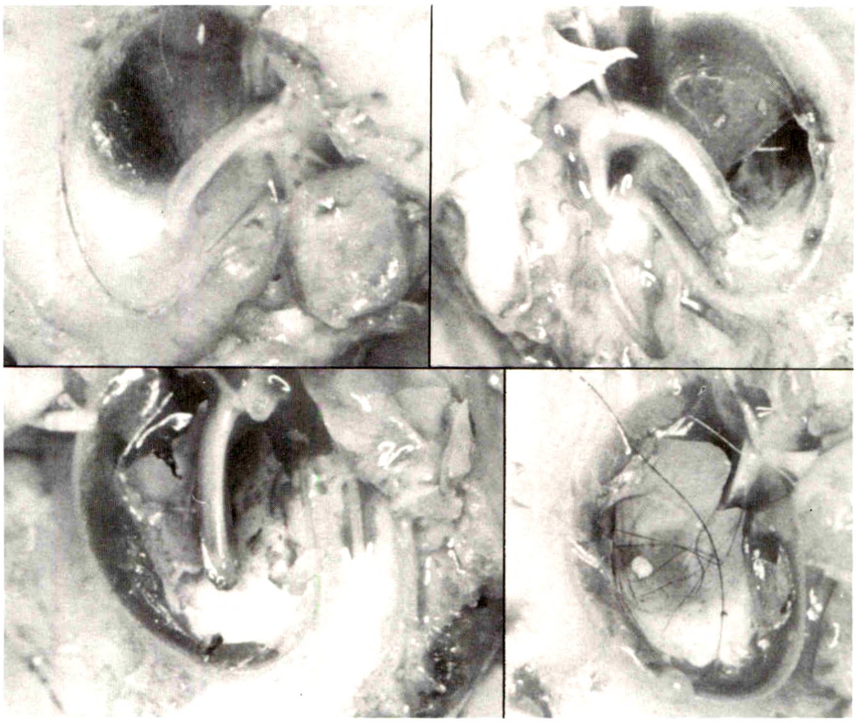


Fig 2. Dog eardrums ruptured by blast, viewed from middle ear.

TABLE 3. PEAK OVERPRESSURES REQUIRED FOR FIFTY PERCENT INCIDENCE OF EARDRUM RUPTURE IN HUMANS

Reference	*Peak Overpressure in Kilopascals (psi)*	*Waveform*
Zalewski[4]	161* (23.0)	Static
Blake et al[3]	101 (14.7)	Fast-rising, incident shock
Blake et al[3]	345 (50.0)	Fast-rising, incident shock, air raid casualties
Hirsch[2]	110 (16.0)	Mostly fast-rising
James et al[6]	57 (8.3)	Fast-rising, incident shock, 3.6-kg charge, 5-ms duration†

*Actually, average pressure for drum rupture.

†See text for other values.

on information from wartime, muzzle blasts, and industrial accidents. The curve predicts a 50% probability for eardrum rupture at about 110 kPa (16 psi) and 1% at just over 21 kPa (3 psi). However, the author stated the threshold for eardrum perforation as the time-honored one of 34 kPa (5 psi).

There has been only one systematic experimental study on the response of the human ear to high explosives-produced airblast.[6] To determine the pressure-impulse criteria for eardrum rupture, fresh cadaver temporal bone specimens were mounted on a 90 x 90-cm flatboard placed on the ground. The pinnae were removed in most cases. The external auditory meatus was flush with the surface. Explosive charges were detonated above the surface, with the ear at normal incidence to the incident shock wave, so that the canal was loaded with reflected pressure. Charges also were placed on the ground so that the ear canal was loaded with the incident side-on pressure. Charge weights were 7.1 g, 57 g, 0.454 kg, 3.63 kg, and 29.1 kg (0.0156 lb, 0.125 lb, 1 lb, 8 lb, and 64 lb, respectively). Some tests were run just with detonators that contained about 1 g of explosive. In addition to free-field pressure-time measurements, others were made with transducers at the eardrum locations. On a few tests, the effect of large and small pinnae was evaluated.

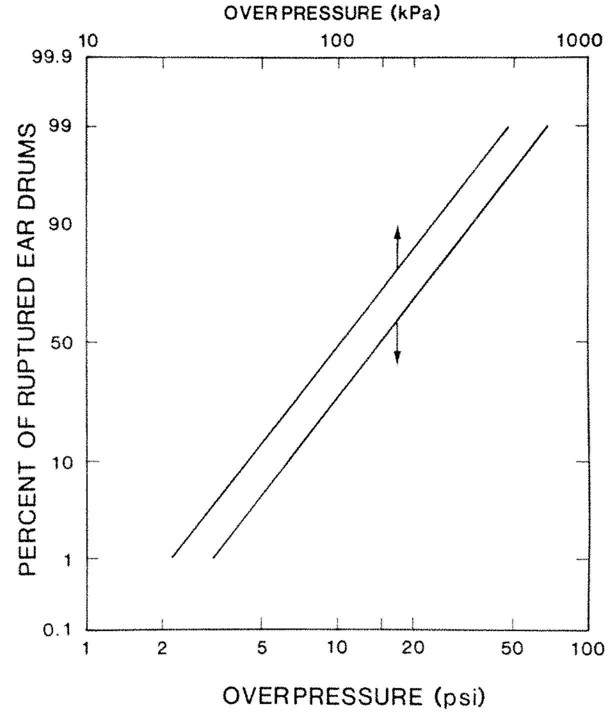


Fig 3. Dose-response curve for human eardrums exposed to fast-rising blast waves. (Modified from Hirsch.[2])

This study was extensive in scope: 29 tests with charges at normal incidence and 16 tests at side-on or grazing incidence. There was a sample of ten ears on most tests. The extent of ear damage was graded as follows. Grade 1 was minor rupture. This included minor slits, and linear disruption of the drum fibers producing a meshlike effect. Grade 2 was moderate rupture and included large tears or multiple small holes or tears. Grade 3, major rupture, was characterized by total disruption of the drum with large flaps of drum. Some were inverted into the ear and some everted. At the higher pressures, there was disruption of the ossicular chain. In two cases, this occurred without eardrum rupture.

Results from the few tests (side-on conditions) with pinnae present suggested that the impulse at

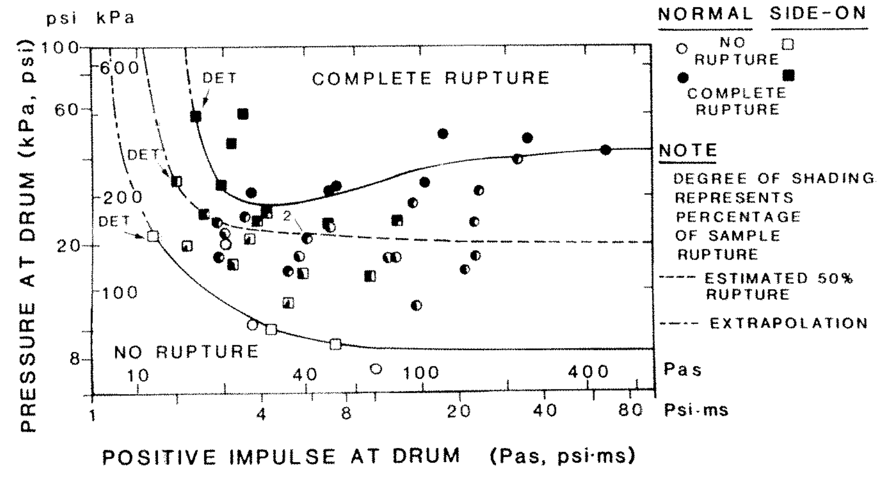


Fig 4. Pressure-impulse rupture criteria. DET — detonation. (Modified from James et al.[6])

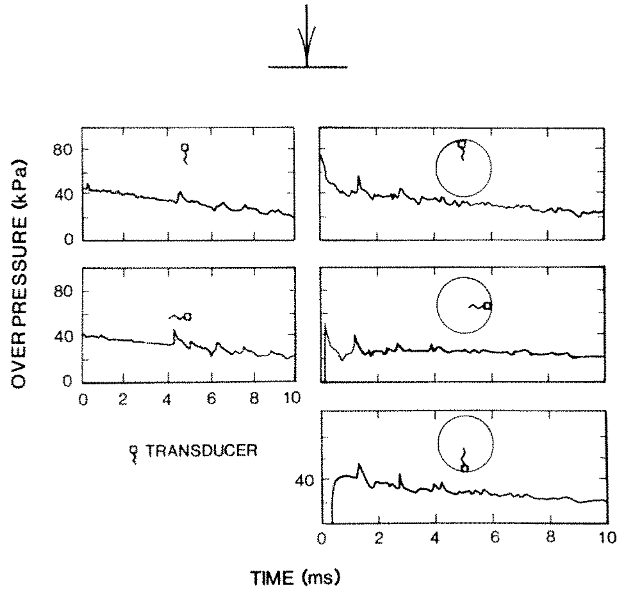


Fig 5. Pressure-time patterns measured on cylinder in shock tube. (Modified from Coulter.[7])

the drum would be about the same without them. Higher pressures were measured when the pinna was back-on to the wave than when it was face-on to the wave, and small pinnae had more effect than the larger ones. At normal incidence both sizes of pinnae produced only a small reduction in the peak pressure and impulse at the drum.

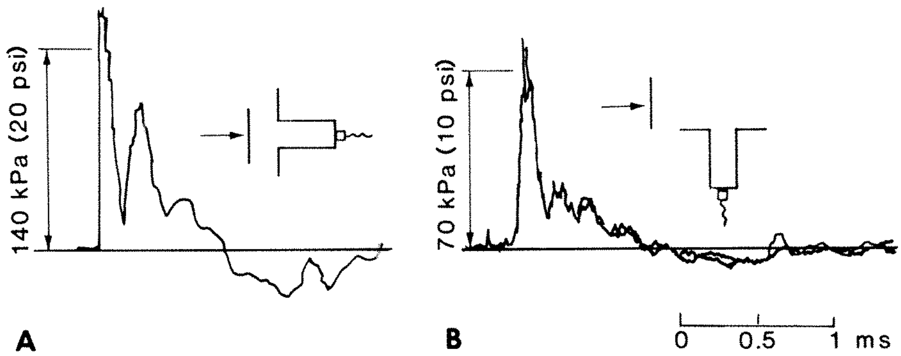
Figure 4[6] shows the percentage of eardrum rupture in each sample as a function of the pressure and impulse at the drum. A 50% rupture curve and curves giving limits for complete rupture and no rupture were drawn through the data points. Minimal incident pressures for eardrum rupture were on the order of 15 to 16.5 kPa (2.2 to 2.4 psi), resulting in 50 to 56 kPa (7.2 to 8.2 psi) at the drum. A P50 of 57 kPa (8.3 psi) (Table 3[2-4,6]) was calculated for the 3.63-kg (8-lb) charge data with the ear side-on. The curves indicate that a peak overpressure of 50 to 56 kPa (7 to 8 psi) and an impulse of 8 Pa/s (1.2 psi/ms) must be exceeded at the eardrum for eardrum failure.

EFFECTS OF ORIENTATION

Orientation of the head with respect to the advancing blast wave affects the magnitude of the overpressure arriving at the tympanic membrane. Pressure-time patterns measured on the surface and incident to a cylinder (Fig 5[7]) are roughly analogous to what may be expected for the head. The pressure wave patterns were taken from the experiments of Coulter,[7] who measured the drag forces and pressures on a cylinder in a shock tube. The illustration in Fig 5[7] shows an incident shock wave of 42 kPa (6.1 psi) measured by a side-on transducer. The face-on transducer shows the reflected shock of 95 kPa (13.7 psi), which decayed rapidly (because of the small surface area of the transducer) to the total pressure level of near 46 kPa (6.7 psi). The difference between the total pressure and the side-on is the dynamic pressure or $Q = 1/2\,\rho V^2$, where ρ is the density of the gas and V is the velocity of the flow. As seen in Fig 5, the ear on the upstream side of the head is subjected to a reflected pressure that is twice the side-on value. At higher side-on pressures, the reflected pressures can be three or four times higher than the side-on. A head facing the blast exposes the ears to the side-on pressure. An ear on the downstream side of the head encounters a fast-rising wave with a rounded peak of about the magnitude of the side-on pressure. The spike seen in the recordings at 1.5 to 2.0 ms is the result of a reflection from the cylinder returning from the wall of the shock tube. The overall duration of the overpressures was about 30 ms.

Pressure-time recordings reported by James et al[6] taken by transducers in place of the eardrum in temporal bones of fresh cadavers are illustrated in Fig 6.[6] With an incident pressure of 43 kPa (6.2 psi), about that incident to the cylinder, about 165 kPa (24 psi) was measured at the drum of the ear normal to the incident shock. At the drum of the ear side-on to the incident wave, about twice the side-on pressure reaches the tympanic membrane. The shock entering the ear canal reflects from the walls and bottom and is intensified. That the reflected pressures measured at the drum for the normal incidence case are higher than that expected from normal reflections measured on a surface agrees with the measurements taken in a duct (Fig 7[6]). We also have observed this effect in our foxhole studies.

Fig 6. Pressure-time patterns measured by transducers at eardrum location. A) Incident wave normal. B) Side-on. (Modified from James et al.[6])



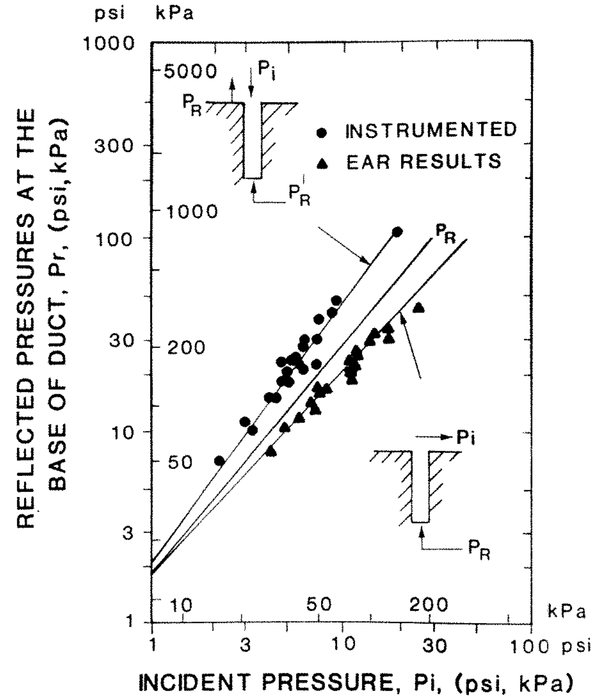


Fig 7. Reflected pressures developed in duct for normal and side-on incident shocks. (Modified from James et al.[6])

DISCUSSION

From the information presented in this report, it is possible to identify the damage parameter(s) associated with eardrum failure for some of the pressure-time patterns. For Friedlander waves (peak pressure at the leading edge of the wave followed by an exponential decay), it is the magnitude of the overpressure. The duration of the overpressure becomes significant when the positive durations are less than 4 or 5 ms.

Maximum overpressures appear to be the damage parameter for eardrum rupture from smooth-rising waves of long duration, specifically for those waves having times to maximum pressure of between 15 ms to several hundred milliseconds. This waveform occurs inside structures having large volume-to-entrance-area ratios when the peak pressure is in the fill phase and shock reflections, if present, are of very low magnitude. Smooth-rising overpressures also occur beneath circumaural ear protectors. The significance of rise times less than 15 ms and short-duration smooth-rising waves has not been defined.

Complex blast waves have two components that must be considered as the damage parameters: shock reflections and the slow-rising increase in pressure. Complex waves occur in structures, vehicles, and enclosures either from the entrance of a blast wave from the outside or from detonations inside them. If the smooth-rising component of the wave dominates, the P50 for eardrum rupture is much higher than if the reflected shocks dominate. In some complex waves, both the reflected shocks at the leading edge of the wave and the peak pressure in the smooth-rising part of the wave are of sufficient magnitude to cause eardrum rupture. In structures with small volume-to-entrance-area ratios, such as foxholes, the reflected shocks predominate and there is an insignificant fill phase. Inside shelters having large volume-to-entrance-area ratios, the fill phase is important, as mentioned above.

In regard to the consequences of eardrum rupture on human behavior or performance, there has been little to go on in the past. It is stated consistently that there is immediate pain, hearing loss of various degrees, hemorrhage, tinnitus, and sometimes dizziness. In wartime, blast victims are not examined for some time following injury, and usually other lesions are given attention first. Victims' immediate reactions to ear injury are not recorded. With the advent of terrorist bombings, more blast victims have received immediate medical attention. In some instances, otolaryngologists have evaluated

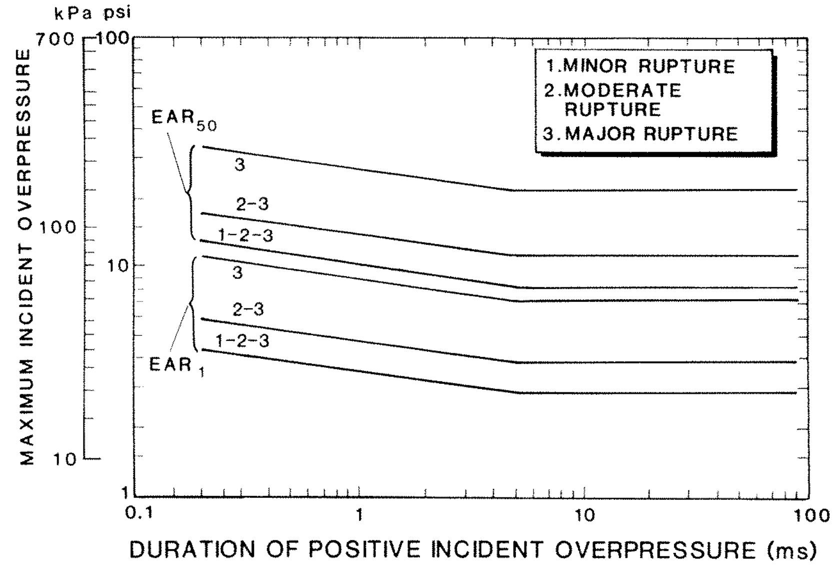


Fig 8. Incident overpressures required for 1% (EAR1) and 50% (EAR50) incidence of three grades of ear injury applicable to humans in freestream.

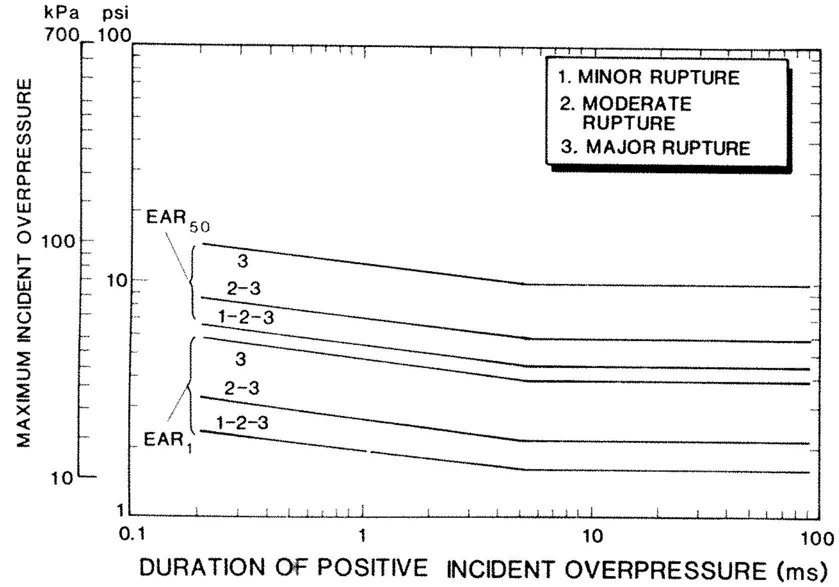


Fig 9. Incident overpressures required for 1% (EAR_1) and 50% (EAR_{50}) incidence of three grades of ear injury applicable to humans against or near reflecting surface.

the severity of the barotrauma and have documented the behavioral consequences.[8,9]

We analyzed the data of James et al[6] in order to obtain the incident overpressures and their durations required to produce a 1% and 50% incidence of the three grades of ear damage described, ie, grade 3 only, grades 2 and 3 combined, and grades 1, 2, and 3 combined. To do so, a probit analysis was run from data for each charge weight and ear orientation. These curves give the overpressure in the incident wave as a function of the positive duration required for 1% and 50% incidence of the three grades of eardrum rupture. Results of the analysis are presented in Figs 8 and 9. Figure 8 applies to personnel in the freestream, and Fig 9 to personnel against or close to a large reflecting surface oriented normal to the incident wave.

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TOWARD A MEASURE OF AUDITORY HANDICAP IN THE ARMY

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The effect of a soldier's ability to hear on the capacity to perform a mission was calculated for a variety of militarily relevant tasks through the use of mathematical models. Changes in hearing can result from organic loss, hearing protectors, the masking effect of noises, etc. The effects were calculated for the detection of sounds of enemy personnel (speech, movement noises) or their equipment (rifle bolt, tank, generator). We also calculated the effects on the ability to control/communicate with troops verbally. The normal ear is highly effective in detecting noises of personnel or their equipment or in understanding speech, even in noise. By contrast, even modest hearing losses and/or the wearing of hearing protectors can have profound effects on military performance, for example, reducing the area that can be monitored acoustically by more than 30-fold or cutting warning times for other sounds by a factor of more than 100. Hearing protectors may have the conflicting effects of protecting hearing while producing unacceptable performance because of their attenuation.

KEY WORDS — auditory detection, auditory handicap, auditory performance, hearing loss.

INTRODUCTION

PROBLEM OF AUDITORY HANDICAP

It is obvious that a soldier's ability to hear is important; however, it is harder to specify in quantitative terms just how a soldier's ability to hear affects his or her ability to perform a mission. We intend to begin outlining a course of inquiry to provide the answers needed, based on what we already know or can calculate.

In essence, we are concerned with auditory handicap, which is traditionally defined as "the disadvantage imposed by an impairment sufficient to affect the individual's efficiency in the activities of everyday living." In may seem like an obvious problem for which there should be more or less exact answers; yet as Ward[1] recently has commented: "...of all the areas embraced by the field of audiology, quantification of degree of auditory handicap and its relation to measurable auditory characteristics is a topic concerning which probably the least agreement exists at international, national and local levels." In the past, the desire to calculate auditory handicap has been driven largely by an interest in indemnification for impairment. The American Academy of Otolaryngology has promulgated a formula for such calculation that is based on loss in pure tone sensitivity at particular frequencies.[1] Given the formula, we can calculate an exact percentage of auditory handicap; however, the connection between the number calculated and "disadvantage...in the activities of everyday living" is extremely tenuous.

The interest in auditory handicap in both civilian and military settings most often has come at the end of a working career when the individual is facing retirement; however, it is the contention of this paper that it would be a serious mistake for the Army to focus its interest at this level. The inability to hear, for any reason, may well be an operational liability affecting accomplishment of the mission and should be factored into the consideration of operational requirements for all systems in which the human being is an element. The inability of a gunner to hear a fire command correctly, the inability of a listening post to detect the presence of enemy personnel, the inability of a squad leader to communicate with the soldiers, or problems in a host of other auditory tasks may represent consequences for performance of the mission that are at least as great as other operational considerations. Were we able to quantify the effect of auditory impairment, it would be possible to factor the handicap into the decision-making process and allow intelligent decisions to be made regarding the design, procurement, and operational use of Army materiel as well as the requirement for hearing on the part of the soldier.

As serious as hearing impairment can be, we hasten to add that it is also conceivable that for some tasks a given hearing loss may not represent a handicap. What we intend is an accurate assessment of performance based on realistic considerations. If a hearing impairment can cause operational difficulties, we need to know about it. If, on the other hand, it does not, then we need to know that, too.

A reduced capacity to hear can be the result of any one or a combination of independent processes; the obvious case is one in which noise exposure has

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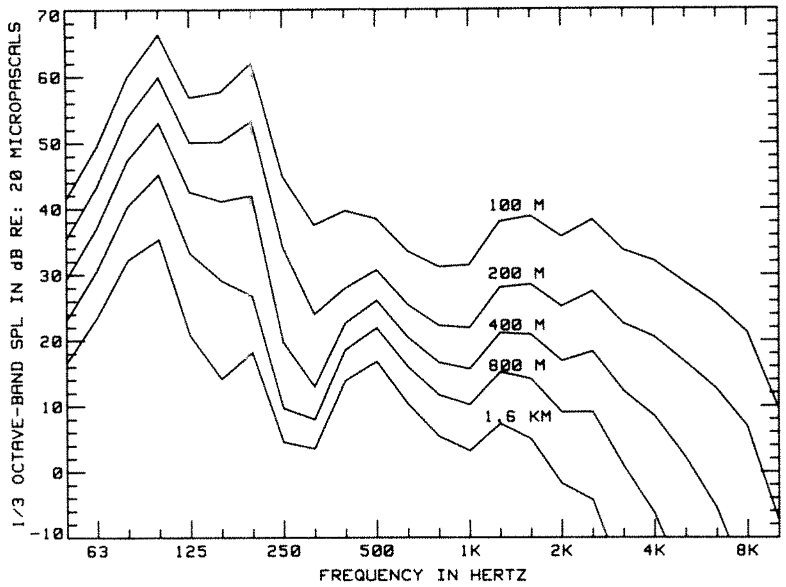

Fig 1. Computed band-pressure level at several distances from 30-kW generator based upon propagation model and measurements at 10 m.

resulted in a permanent change in the ear. In a less severe case, noise might produce a transient loss from which the ear will eventually recover but which is nevertheless an impairment for the interim. Other sources of "impairment" are nonorganic. Noises produced by equipment such as generators or armored vehicles may lessen the ability to hear because they mask auditory information. Or alternatively, soldiers may be forced to wear hearing protectors or other headgear made necessary by operational requirements, which in turn produces auditory impairment.

HANDICAP IN ARMY CONTEXT

The Army also has some special concerns in the matter of auditory handicap that may not have parallels in the civilian world. In the civilian world, the overwhelming interest has naturally been in the ability to understand speech. However, in a military setting (and even to some degree in a civilian setting), being able to hear nonspeech sounds can be vitally important.[2] Katzell et al,[3] in a survey of combat recognition requirements conducted after World War II and the Korean conflict, showed that enemy personnel were the most important target for all types of military units in the field. Furthermore, they were most often detected by the noise they or their equipment made. Interviews with Vietnam veterans produced a similar finding. For example, the approach of enemy personnel would often be revealed by the noise made in parting dense foliage. There are analogous situations in the civilian world as well, eg, persons with hearing losses may have to give up hunting because they can no longer hear the game.

It is becoming apparent that if we are to understand auditory handicap it will be necessary to expand our focus from the understanding of impairment of speech perception to include a wide range of auditory issues and their impact on the soldier's efficiency in his or her military activity. Thus our focus must expand to include an analysis of the specific things we do in daily living and an assessment of what role the sense of hearing plays in them. In general, we know much more about the role of hearing in everyday living. We can probably predict the percentage of words a particular subject will hear correctly in some environment, but what impact will that have on task performance? What is the consequence of an incorrect perception? Can the individual with an impairment work effectively with other people? The prospect of this level of analysis for all the activities of daily living in the Army is truly staggering and is probably one of the reasons that consideration of auditory handicap has been confined largely to the impairment of speech perception.

On the other hand, as massive as the problem of establishing auditory handicap is, it should be possible at least to make a beginning. The need for such an effort was recognized in our laboratory some years ago, and a modest beginning was made by examining the problem of detecting the sounds made by personnel, eg, movement through a sapling thicket, footfall in grass, closing a rifle bolt.[2] We are now in the process of expanding our efforts in this area and, with new data on sound propagation and detection, will try in this paper to relate the ability to hear to the performance of everyday living of a member of the infantry.

PROCEDURES

MODELS USED IN CALCULATIONS

In the development that follows, we use mathematical models of both sound propagation and auditory detection that have been developed in our laboratory. The details have been reported else-

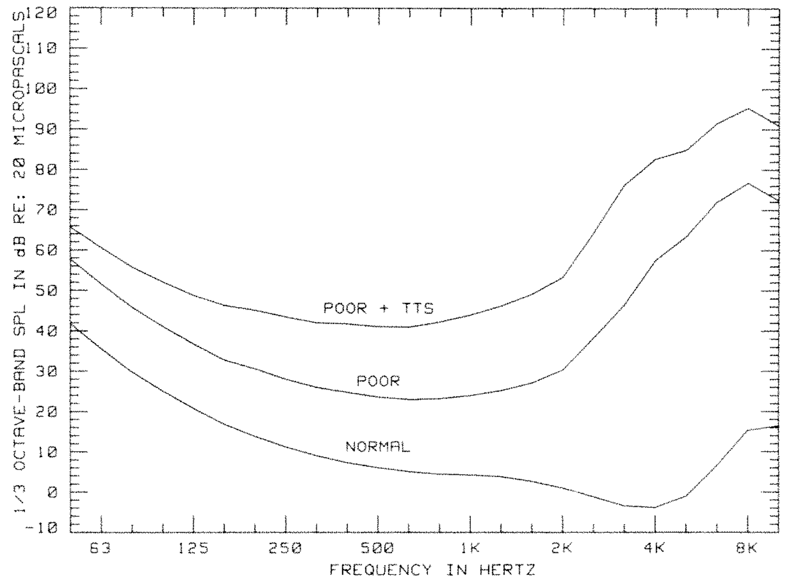

Fig 2. Assumed hearing levels for soldiers with normal hearing, poor hearing, and poor hearing plus temporary threshold shift (TTS).

where.[4] Both the propagation and detectability models will be summarized briefly here, but additional details are included in the Appendix.

As used in this study, the propagation model accounts for three effects: geometric spreading (progressive loss in intensity due to expansion of the wave front), atmospheric absorption, and ground effect with atmospheric turbulence (losses due to interactions with the ground surface). Many other factors affect sound propagation, such as the presence of barriers or foliage, or reflection due to wind or to air temperature. Because these might or might not exist in operational situations, these factors have been excluded from the calculations.

The effect of the propagation model on the spectrum of a sound is complex, in keeping with the nature of real propagation processes. Figure 1 illustrates the spectrum of a generator as it would appear at 100, 200, 400, and 800 m, and 1.6 km. It is apparent that in addition to a change in level, the shape of the spectrum also changes as the sound propagates. The high frequencies tend to be lost through atmospheric absorption, and the low frequencies are altered by ground effect.

The detectability model brings with it another class of considerations, specifically the listener variables. The model naturally includes the listener's threshold for pure tones and corrections for the listener's judgment processes as developed in the Theory of Signal Detectability.[5]

We were interested especially in the differences in performance that are a function of the condition of the ear. We used three levels of hearing acuity in our calculations: normal hearing, poor hearing, and poor hearing complicated by the addition of a temporary threshold shift (TTS) from noise exposure or the wearing of a hearing protector.

The values used for normal hearing in our calculations are those of hearing sensitivity in the free field for young ears.[6] The values used for the ear with poor hearing were taken from a survey of hearing in the combat arms.[7] The values used were those for men who had been in the infantry 17.5 to 22.4 years and are the levels exceeded by 25% of that age group, ie, 25% of that group had hearing that bad or worse. There was essentially no difference in hearing levels between the armor, artillery, and infantry branches surveyed.[7] Figure 2 presents the sensitivities used for both the normal ear and the poor ear. The third curve in this Figure represents the realistic possibility that an ear also might be suffering a temporary hearing loss as the result of noise exposure. Specifically, we calculated the TTS that would result in an unprotected ear riding for 1 hour in an armored personnel carrier (113 dBA sound pressure level) and added it to the threshold of the poorer hearing ear.

In making calculations of auditory performance, we have simplified the situation by treating a noise-induced hearing loss simply as an elevated threshold, ie, as a normal ear receiving a weaker signal. In fact, Plomp[8] has shown that a noise-induced hearing loss consists of two components, an attenuation component and a distortion component. For an impaired ear, for example, a speech signal might well be above threshold, but it might not be "clear." The practical implication of ignoring the distortion component is that the handicapping effect of a particular loss will be underestimated.

There is an additional type of hearing loss that should be considered in the military context, specifically that of a ruptured eardrum resulting from an explosion. We know from working with animal ears that the loss of an eardrum in and of itself produces conductive changes in the middle ear that vary as a function of the size and position of the perforation. The conductive loss can amount to less

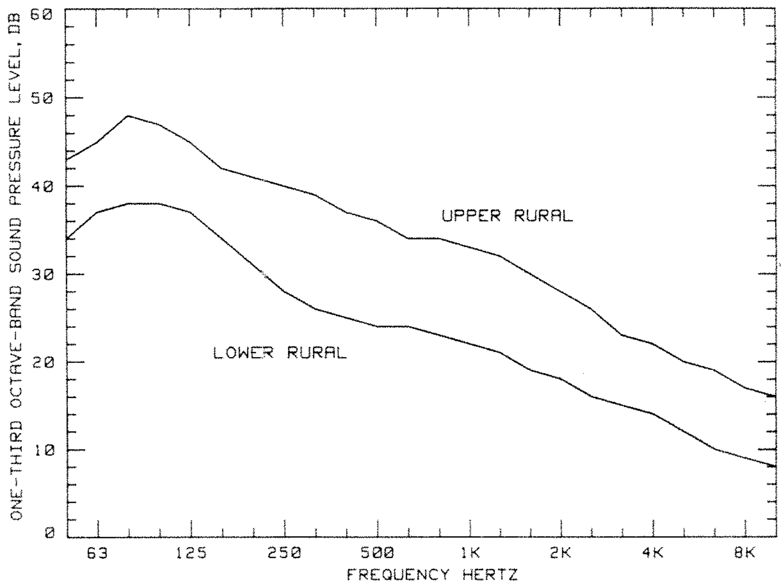

Fig 3. Upper and lower rural background noise levels (shaded zone).

than 20 dB for a 20% loss of area and about 40 dB across all frequencies when the eardrum is 80% to 100% removed.[9] An acoustic impulse capable of rupturing the eardrum is also likely to produce at least some additional TTS as well, which could easily add an additional 40 dB or more of sensorineural loss. Given losses of this size (80 dB or more), the ear is essentially totally deaf. For example, victims of terrorist bombings report that following the explosion (in a room), they could see people's mouths moving but could not hear anything. At least for the short term, such ears are simply not functional. But for smaller losses, the effects of the perforation of an eardrum would be the same as for other sources of impairment.

The auditory world is always present. In making the calculations we presume one of two ambient noise backgrounds typical of those found in rural areas at varying distances from man-made noise sources[10] and assumed to be fairly typical of the quiet periods on a battlefront. These levels are presented as the boundaries of a shaded zone in Fig 3. We have used both the upper and lower limits of this zone individually in our calculations. In the text they are referred to as upper rural (UR) and lower rural (LR) background noise levels.

RESULTS

GENERAL COMMENTS

It cannot be overemphasized that the performance data discussed below are calculated almost exclusively from the models and consequently incorporate a very large number of assumptions. They are believable and are in fact the best estimate we have, but they should be verified empirically. A mitigating consideration was that in most cases, our interest was in the change in performance as a function of hearing level. Thus, although the absolute values might not be entirely accurate, the relative values are probably close to the true ones.

In pilot experiments, we have tried to verify the models empirically, and the results have been very encouraging. The largest problem is getting a really quiet (or known) background sound. Ambient sounds in real situations tend to be highly variable; consequently, even though they have been measured carefully at one time, the conditions at the moment of detection may differ from the measured background. In the "best of all possible experiments," the ambient noise and atmospheric conditions should be captured at the moment of detection. In the pilot experiments with normal and protected ears we have tried to detect conversational voice, shouted voice, a rifle magazine being inserted, the rifle bolt closing, and a generator. The calculated detection ranges have agreed reasonably well with the actual detections, usually within 30% to 40%. For detection tasks, errors of this size are relatively small, ie, all parameters must be within 1 or 2 dB for results to come this close.

The data are presented in Figs 4 through 9, with the sensitivity of the ear described as normal, poor, or poor + TTS plotted on the abscissa. This presentation is irregular, in that the abscissa represents only an ordinal scale and not a ratio scale as might be assumed. Likewise, the lines connecting the data points are only indications of which points go with one another. This type of presentation, while somewhat irregular, does make it easy to interpret the data.

DETECTING ENEMY SOUNDS

Because enemy troops often reveal their location by the noise they or their equipment makes, detection of such sounds is critical.

Detecting Sounds of Enemy Personnel. One characteristic of humans is that they do a lot of ver-

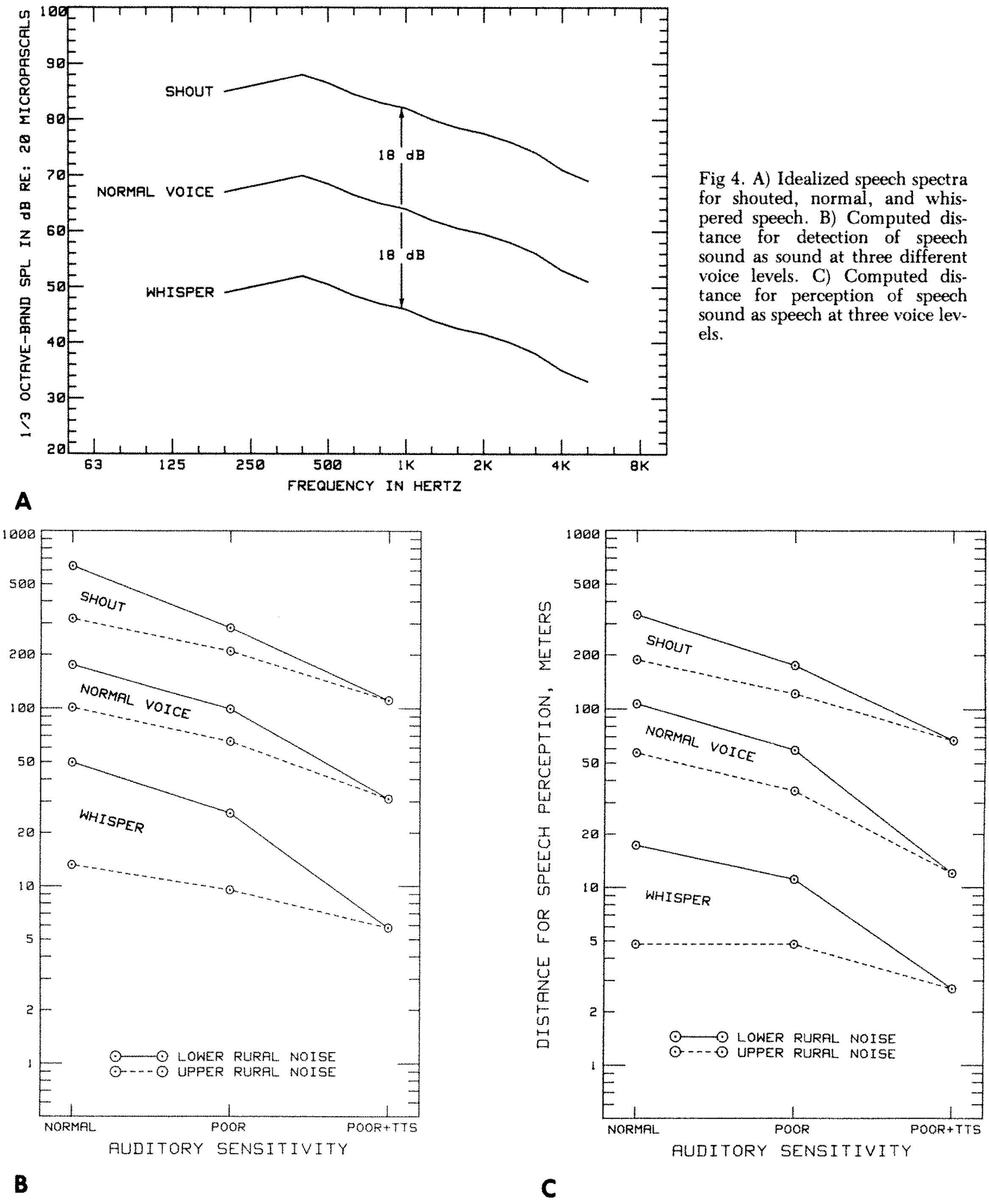

Fig 4. A) Idealized speech spectra for shouted, normal, and whispered speech. B) Computed distance for detection of speech sound as sound at three different voice levels. C) Computed distance for perception of speech sound as speech at three voice levels.

bal communicating; therefore, human speech is a prime target for detection. Detection distances have been calculated for three levels of vocal effort: a leader might be shouting commands at the soldiers, the soldiers might simply be walking and talking as they go, or when trying to observe noise discipline they might be whispering to one another. Two different listening criteria were used in the calculation: 1) simple detection of the presence of some sound and 2) detection and identification of the sound as speech (not yet intelligible). According to Egan,[11] speech that can just be detected must be 8 dB more intense to reach the level at which it can be identified as speech. The speech spectra used are presented in Fig 4A, and the calculated distances for detection and perception of the sounds as speech are presented in Fig 4B,C. The range over which voices can be detected with a normal ear in an LR background noise is relatively great. Decreases in hearing sensitivity produce corresponding reductions in detection distances. The detection distances for the poor ear are about one half those for the normal ear, and for the poor ear with TTS, only about one sixth those of a normal ear.

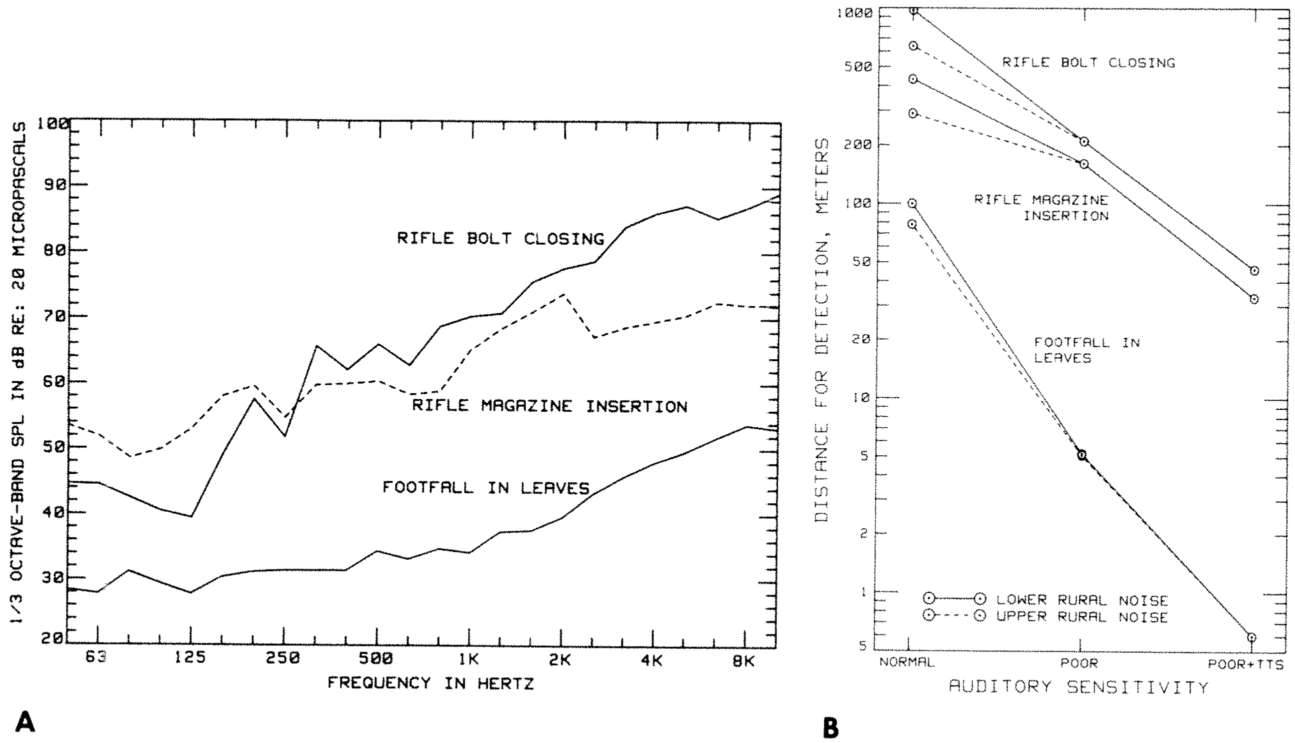

Fig 5. A) Band-pressure level of several sounds made by personnel at 1 m. B) Computed distance for detection of several sounds made by personnel.

The data for identification of the sound as speech are presented in Fig 4C. As expected, the absolute distances are about one half as far as for simple detection. For both normal and poor ears, the detection distances are less in the UR background noise. For a poor ear with TTS, its own threshold is high enough that the background noise makes no difference.

The practical implication of these detection distances is that a normal ear can monitor four to 36 times as much area as the ears with poorer sensitivity, or can provide two to six times as much warning time of the approach of enemy troops.

Detecting Nonspeech Sounds of Enemy Personnel. The equipment personnel carry and their movements through various types of terrain also make noises that need to be detected by the sentry or listening post. We calculated detection distances for the noises of a rifle bolt closing, a rifle magazine being inserted, and walking in leaves. The spectra of these noises are presented in Fig 5A, and the detection distances are shown in Fig 5B. These sounds have considerable energy in the high frequency region; consequently, it is not surprising that ears with losses in the high frequency region do especially poorly in detecting these sounds. It is impressive to see that a normal ear is capable of detecting the sound of a rifle bolt closing at almost 1,000 m in an LR background noise (Fig 5B). In contrast, a poor ear with a TTS can manage the same detection at only 46 m, more than a 20-fold decrease. The magazine insertion is quieter, but the result is the same: 433 m versus 33 m for the same ears. Likewise, for the same conditions, the noise of walking in leaves yields detection distances of 100 m versus 0.6 m. In practical terms, the soldier with a normal ear would have almost 2 minutes' warning of the approach, the person with a poor ear would hear the approach when the enemy was five steps away, and the same individual with a TTS would not hear it at all. For such sounds, a normal ear can monitor an area 200 to 400 times as great as an impaired ear, or provide 13 to 20 times as much warning of the enemy's approach. The soldier with a poor ear and a TTS indeed would be a detriment to the unit if it had to rely on him or her to warn of the enemy's approach.

Detecting Heavy Equipment Sounds. Tanks and generators are targets of special interest to the military. Tanks are an obvious threat, and generators are important because they reveal high priority sites such as missile locations and headquarters. The spectra for these sounds are presented in Fig 6A, and the detection distances in Fig 6B. The sounds have most of their energy at low frequencies and are fairly intense; therefore, they propagate relatively well and can be detected at relatively long distances. For both normal and poor ears, the background noise limits detection of a moving tank to somewhat more than 6 km. A poor ear with TTS would detect it at about 1.8 km: much less distance, but not as much less as for other sounds not masked by the background noise. Obviously, in a noisy background almost all ears will detect at the same

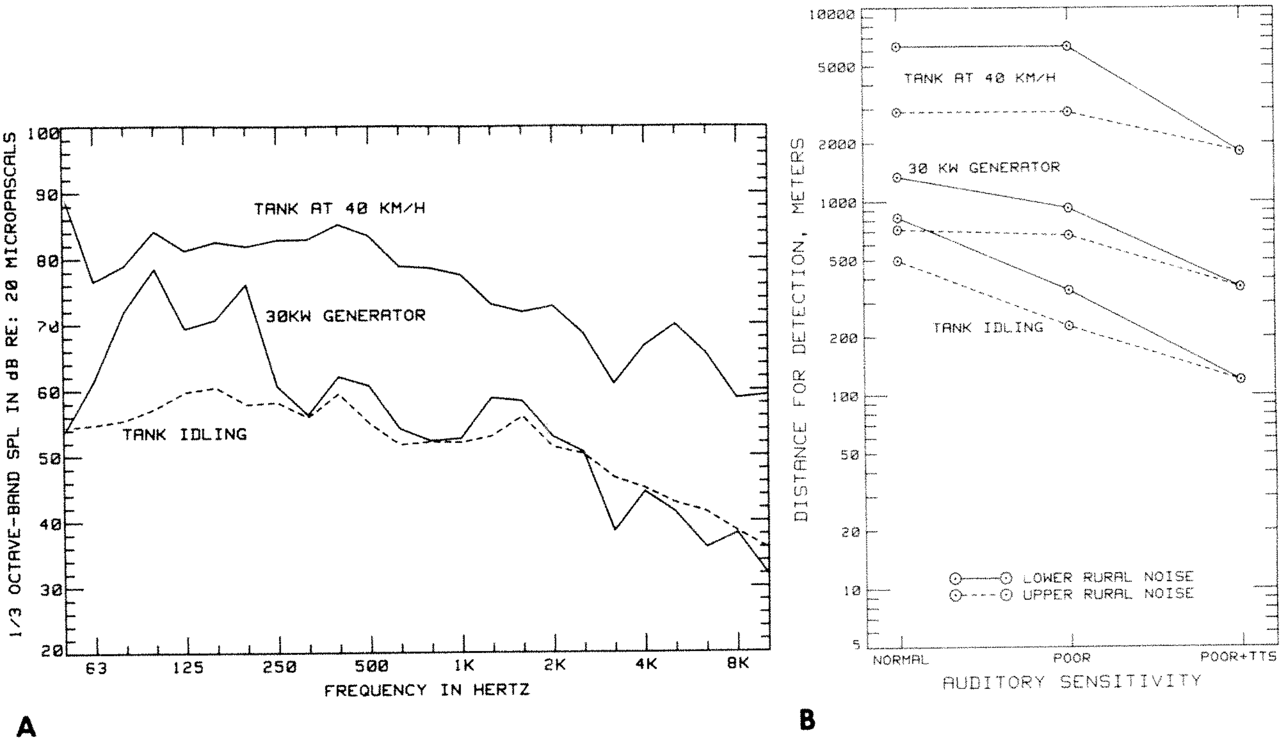

Fig 6. A) Band-pressure level of several sounds made by heavy equipment at 25 m. B) Computed distance for detection of several sounds made by heavy equipment.

time, because the noises are all masked by the ambient noise. Even so, a normal ear detects at more than 3.5 times the distance of the impaired ear. The same general pattern holds for both the noise of the tank idling and the generator. In all cases, the worst ear is limited by its own high threshold. For such sounds, the normal ear monitors 12 times the area and gives 3.5 times the warning of the worst ear.

SPAN OF CONTROL EXERCISED

It may be true that visual cues such as hand and arm signals or flares can be used to control soldiers in the field; however, in practice they are not really effective (in combat, cover and concealment are sought by all; being seen is a dangerous business). Therefore, for the leader expected to exercise personal control, the problem is largely a function of maintaining auditory contact.

Distances Over Which Good Control Can Be Exercised. We calculated the distances over which intelligible communication can take place using different voice levels. The results are presented in Fig 7. As one might expect, better ears can hear further than impaired ears at all voice levels. A shout can communicate about 100 m with a normal ear in the LR background noise, about 40 m with a poor ear, and less than 5 m for that ear with a TTS. A similar change in communication distance takes place for all voice levels.

A practical implication is that maintaining voice contact with a squad after dismounting from a ride in an armored personnel carrier would be difficult and next to impossible for a platoon-sized unit. It is an interesting sidelight to note that the shouts required to control such a platoon would be detected by a normal ear more than 600 m away. Stealth and poor hearing are inimical to one another.

Communicating at Fixed Distance. Another way of looking at the problem is to consider the case of the individual in the crew-served weapon who needs to hear fire commands, yet also should be wearing hearing protectors because of the impulse noise produced by the weapon. We assumed a 10-m communicating distance and elevated voice levels (raised voice and shouts) as well as highly effective (E-A-R) and standard (V51-R) hearing protectors. Then we calculated the Articulation Index (see Appendix) and interpreted it as a percentage error in different types of communication (standard phrases indicative of fire commands, or first-time sentences typical of normal communication). The results are presented in Fig 8 for the two different background noise levels.

Individuals with normal ears can communicate almost perfectly with and without hearing protectors and in either background noise. Those with poor ears will get better than 90% of the information correct as long as no hearing protector is worn. If a moderately effective protector (V51-R) is worn, the poor ear will get only about 72% of standard phrases correct, and 37% of first-time sentences. The situation is worse if a highly effective protector (E-A-R) is worn, because the poor ear gets nothing

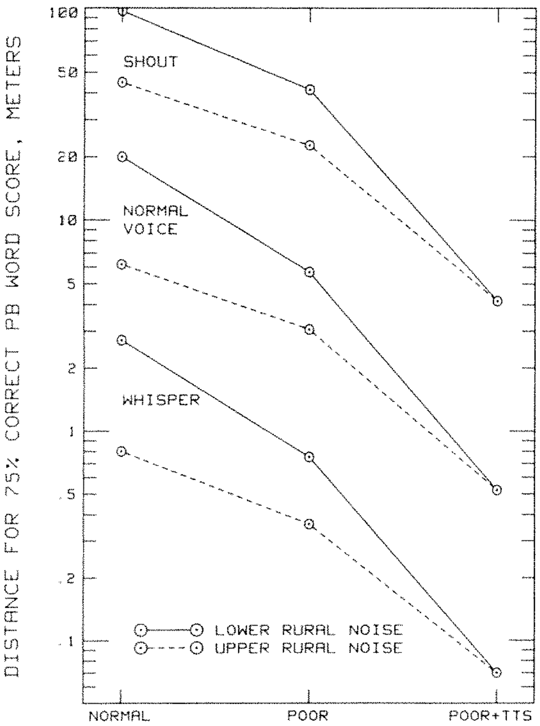

Fig 7. Computed distance for obtaining PB speech intelligibility score of 75% at three different voice levels.

correct. Of course, a poor ear with TTS (not plotted), with either plug, also gets nothing correct.

Given that there are relatively few perfect ears, these calculations suggest that the artillery crew is in a dilemma. If they wear hearing protectors (as regulations require), they will have considerable difficulty hearing fire commands, make more errors, take longer to get rounds off, etc. If they do not wear protectors, then they will suffer hearing losses and ultimately will be unable to hear anything. From their standpoint, an optimum solution would be to design a less hazardous weapon or provide nonlinear hearing protectors that would exclude only the loud sounds.

Communication in Noise. The noise inside combat vehicles not only produces TTS, but also affects communication inside the vehicle. Communication within track-laying armored personnel carriers consists of both electrically aided communication between crew members (the driver and the commander) and person-to-person communication between squad members. The crew members communicate over an intercommunication system wearing a noise-attenuating tanker's helmet, while squad members may or may not wear hearing protectors.

The intelligibility of electrically aided speech was computed for communication between the driver and commander of both a standard M113 armored personnel carrier and a quieter one meeting the Army's suggested noise limits for vehicles of this type (MIL STD-1474B) (100 dBA). At 40 km/h, the standard M113 produces 113 dBA. Intelligibility for both sentences heard for the first time and the standardized phrases is shown in Fig 9A.

For the standard M113 vehicle, crew members with normal hearing can understand sentences 80% of the time, with this score decreasing to 29% for an individual with poor hearing with TTS. Of course, intelligibility is substantially better if communication is accomplished by using standard phrases. However, there are many emergency or unexpected situations in which this is not possible.

An attractive approach to improving intelligibility is to reduce the masking noise of the vehicle. At a level of 100 dBA, we see from Fig 9A that intelligibility for both standard phrases and normal sentences approaches 100% for individuals with normal hearing. Even with poor hearing and TTS, in-

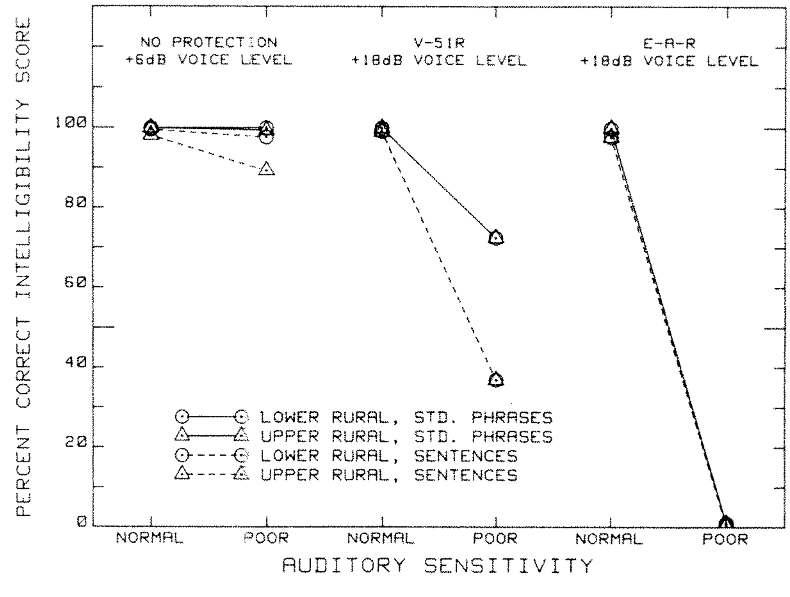

Fig 8. Computed speech intelligibility of standard phrases and first-time sentences at 10 m in two different background noise levels with and without hearing protectors for normal and poor hearing.

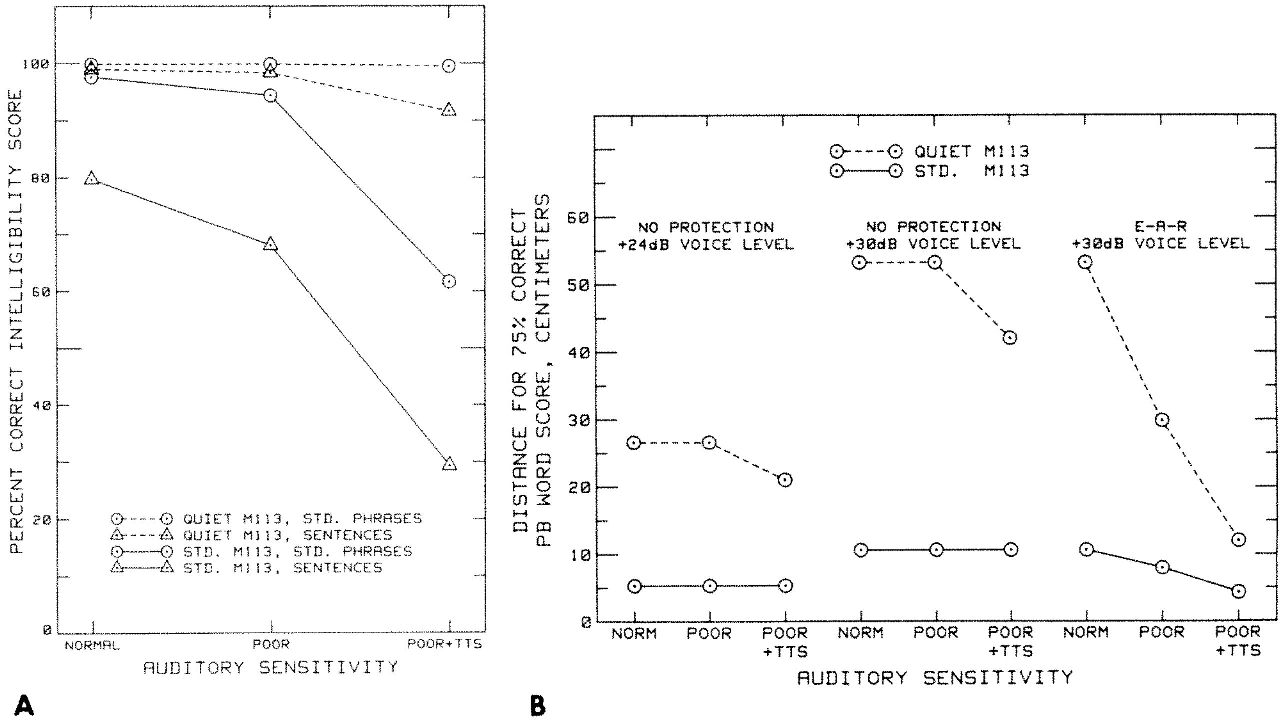

Fig 9. A) Computed speech intelligibility of electrically aided communication for standard phrases and first-time sentences for three different hearing levels in standard and quiet M113 armored personnel carriers. B) Computed distance for obtaining person-to-person PB speech intelligibility score of 75% for three different hearing levels with and without hearing protection in standard and quiet M113 armored personnel carriers.

telligibility is greater than 90%.

For the squad members in the crew compartment, the noise at 40 km/h prevents even intensely shouted communication at more than a few centimeters. Talker-to-listener distances required to produce 75% intelligibility were computed for both a standard and a quiet M113. Figure 9B shows that in a standard M113, personnel must be within 10 cm to communicate even with an intensely shouting voice (normal voice level plus 30 dB). This Figure also shows that when no hearing protectors are worn, persons with poor hearing will do as well as those with normal hearing, because speech signal-to-noise ratio is determined by vehicle noise rather than by hearing threshold. In a quiet M113, however, the communicating distance is increased by a factor of 5 to 52 cm for individuals with normal or poor hearing. Those individuals with poor hearing plus a TTS will not do as well, because their perception of speech is limited by their threshold of hearing rather than the vehicle noise. However, when the E-A-R plug is worn, personnel with normal hearing will understand speech as well as those not wearing protectors, whereas those with poor hearing will do significantly worse.

The practical implication of this analysis is that vehicle noise reduction is the single most effective method of improving communications. A byproduct of this approach might be that aural detection distance of the vehicle would be reduced concomitantly.

DISCUSSION

For the member of the infantry, we have managed to calculate a few numbers that predict his or her performance in several practical situations. The calculations should be verified empirically, but for the moment let us suppose that they are essentially valid. It is clear that auditory impairment can have serious operational influences and may well affect the accomplishment of the mission. What can we now say about auditory handicap? How much is too much and how much is tolerable?

One observation that is helpful in making a value judgment came in a conversation with an infantry officer. He commented that although one might conduct firing exercises with troops wearing hearing protectors when they fired from fixed positions, "no one in his right mind would consider having troops wear hearing protectors while on a range in which they move and shoot." It could, therefore, be argued that the auditory impairment represented by the attenuation of an earplug is a significant handicap. It happens that the temporary hearing loss from riding in the crew compartment of an armored personnel carrier for an hour at 32 mph is of the same magnitude as the V51-R earplug attenuation. It is also true that permanent hearing loss of the ear of the 25th percentile soldier with 17.5 to 22.5 years of service is of the same magnitude. For infantry personnel, that degree of hearing impairment probably should be considered handicapping.

From the standpoint of the commander in the field, it is reasonable to suppose that any change in his or her personnel's ability that would result in a 50% reduction in intelligence regarding the enemy would be unacceptable, yet we have seen that even modest hearing losses can reduce the information to less than 1% of what it would be for a normal ear, or warning times of crucial minutes or seconds might be reduced by a factor of four to 20. Control problems would keep squads from spreading out, perimeter security would be affected, error rates in communication would rise, and artillery rounds would take longer to be fired and even might be fired at incorrect coordinates.

From the standpoint of the materiel developer, it would appear that current weapons are too noisy. Vehicles such as the armored personnel carrier will produce performance penalties for the units using them. Weapons that require hearing protection are subject to the same criticism. Either the personnel wear the protectors and have problems in detecting and communicating, or they do not wear them and will develop performance problems when the weapons are used.

This paper only begins to try to establish the true effects of auditory handicap and is characterized by many omissions. For example, we have not covered such considerations as the localization of sounds or their identification. Moreover, hearing losses usually are accompanied by feelings of tension, stress, and insecurity,[12] and lead to personality changes that would have a profound effect on group cohesiveness, morale, etc. The common wisdom is that a hearing loss changes a well-adjusted person into an unhappy recluse. Such effects may be extremely important to the functioning of a military unit.

On the other hand, we have shown in a preliminary fashion that auditory impairment translates into a calculable handicap for the performance of military duties. Presumably, there are civilian parallels as well. Given more information of this type, it is conceivable that admission and retention standards for various military occupational specialties could be affected, as well as the standards and policies for the design, production, and use of materiel.

SUMMARY

Through the use of mathematical models, we have calculated the effect of a soldier's ability to hear on his or her capacity to perform a variety of militarily relevant tasks. Changes in hearing that can result from organic loss, the wearing of hearing protectors, the masking effect of noises, etc, can have a profound effect on performance, producing a militarily significant handicap. The normal ear is highly effective in detecting noises produced by personnel or their equipment or in understanding speech even in noise. By contrast, even modest hearing losses and/or the wearing of hearing protectors can have profound effects on military performance, for example, reducing the area that can be acoustically monitored by more than 30-fold or cutting warning times for other sounds by a factor of more than 100.

This effort at calculating handicap has not been definitive, but it has shown in a preliminary way that it is possible to quantify the effect of a hearing loss and that such information could be used in the establishment of job descriptions, in standards for acceptance and retention of personnel, and in the specification of acceptable noise levels for materiel.

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APPENDIX

The propagation model accounts for three effects: geometric spreading, atmospheric absorption, and ground effect with atmospheric turbulence. Geometric spreading refers to the reduction in sound pressure with distance from a source due to the energy's spreading over an increasingly large area. The reduction to be expected for this reason (once beyond the near field) is 6 dB per doubling of distance or 20 dB for a tenfold increase in distance. The second effect, atmospheric absorption, is the result of the interaction of sound with oxygen and nitrogen molecules and water vapor during propagation through the atmosphere. The result is a complex pattern of loss that depends on the frequency of the sound, the temperature, and the relative humidity. The losses can amount to 100 dB or more per kilometer, although typical losses are on the order of 5 or 10 dB/km. These relationships appear in ANSI.[13] Finally, ground effect is the result of the interaction between the sound wave traveling directly from the source to the receiver and the wave that reflects from the ground. When the wave hits the ground, it is changed in complex ways as it is reflected. The interaction of the direct and reflected waves produces both interference (reductions of as much as 20 dB) and reinforcement (increases of as much as 6 dB). This interference is dependent upon the acoustic characteristics of the source, the source-to-listener distance, the acoustic characteristics of the reflecting surface (flow resistivity), and the source and listener heights.[14-16] In addition to these parameters, the computation includes the nonhomogeneity of the atmosphere (turbulence)[17] and is computed by one-third-octave bands.

Many other factors affect sound propagation, such as the presence of barriers or foliage, or refraction due to wind or to air temperature. Because these might or might not exist in operational situations, these factors have been excluded from the calculations.

The detectability model brings with it another class of considerations, specifically the listener variables. The model naturally includes the listener's threshold for pure tones and corrections for the listener's judgment processes as developed in Theory of Signal Detectability (TSD).[5] In TSD terms, we assume a hit probability of 50%, a false alarm rate of 1% (corresponding to a d' of 2.32), and an efficiency of 40%, which is what one might expect from a well-motivated listener.

The detection model was designed for use with continuous sounds; however, for our present purposes we wished to calculate detectability of transient sounds as well. For sounds up to about 250 ms long and for the purpose of detection, the ear acts as an energy integrator.[18] Therefore, for the transient sounds (rifle bolt closing, magazine insertion, and walking in leaves), energy was integrated for 250 ms, and we calculated the level that would have had to be present for the full 250 ms to contain the same energy. This quantity then was used in the detection program.

Where we have computed speech intelligibility, we have calculated the Articulation Index (AI) according to the procedures in ANSI.[19] We assume the acceptable intelligibility is achieved at an AI of 0.5 (equivalent to a PB test score of 75%). Normal speech is assumed to have an overall long-term root-mean-square level of 65 dB. Shouted and whispered speech are assumed to have a level 18 dB more and 18 dB less than normal speech, respectively. An intense shouting voice is assumed to have a level 30 dB greater than normal speech.

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USE OF MODELING IN PREDICTING TYMPANIC MEMBRANE RUPTURE

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A bioengineering model of the response of the tympanic membrane to air blast loading is proposed as a means of developing Damage Risk Criteria for human exposure to impulsive noise. The model incorporates known physical properties of the tympanic membrane and predicts the magnitude of tissue stresses that occur under various blast conditions. Observed eardrum rupture in cadavers agrees well with the prediction of critical stresses within the tissue.

KEY WORDS — bioengineering, blast injury, modeling, tympanic membrane rupture.

INTRODUCTION

The goal of prediction is to provide a means of estimating the onset and severity of blast injury over a wide range of circumstances. For the methodology to be useful in practice, it must use environmental parameters that can be measured easily, unambiguously, and in the absence of the biologic system. Conversely, it must be able to estimate injury in sufficiently specific terms so that meaningful action can be taken for treatment or protection.

Currently, the primary method for predicting nonauditory injury due to blast waves uses empiric data obtained from animal tests. The occurrences of injury are plotted on the coordinates of maximum incident pressure and positive pressure impulse (Fig 1[1]). From the distributions produced in this way, regions can be identified that can be labeled "safe" and "hazardous," with an area of transition in between.

When large animals are used that have organ structure similar to that of humans and when the environmental conditions are similar to those for which prediction is needed, the resulting Damage Risk Criteria (DRC) can be applied directly to human exposure. Of course, the validity of this procedure depends upon the degree of similarity involved.

Need for More Complete Description. In order to design for the protection of humans exposed to blast and to plan for their treatment, a more complete description of the relation of the environment to injury is needed. Those aspects are discussed below.

First, as the animal data indicate, there is considerable variation in the occurrence of injury at a particular blast condition. Since these tests are performed under well-controlled circumstances (known charge weights and distances), it is unlikely that the variation is in the environment. Rather, the variability between individuals is probably the cause. Therefore, the statistical nature of the biologic system must be incorporated in the prediction process if assessment of risk in a population is to be achieved.

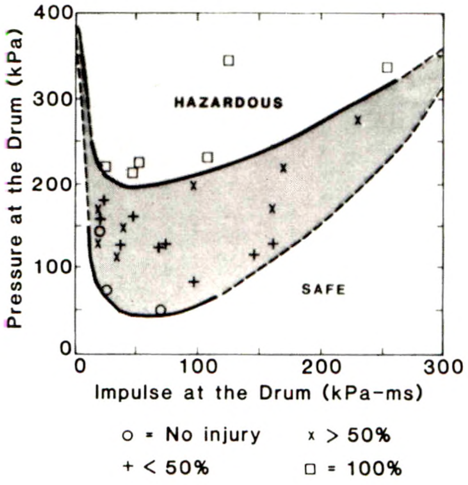

Fig 1. Example of Damage Risk Criteria based on data collected by James et al.[1] Regions that are clearly hazardous and clearly safe can be identified, but their extrapolations to conditions beyond experimental data or to other species is less clear.

Second, there is need to extend the present DRC predictions to complex wave conditions. In studies of blast injury to other air-containing organs, it has been shown that reverberation can lead to injury at pressure levels considerably below those that cause injury in the free-field. There has been speculation on how to translate a complex field into an "equiva-

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REPRINTS — James H. Stuhmiller, PhD, 11011 Torreyana Rd, San Diego, CA 92121.

lent" simple wave, but any such procedure will have a considerable amount of uncertainty associated with it unless it can be justified on more fundamental grounds.

Third, the present DRC can predict only the gross aspects of the injury itself. The location and nature of the damage go beyond the simple representation. For effective application of prediction to triage decisions, it is necessary that a more specific prediction be made that also combines the individual variability mentioned earlier.

Occupational situations require prediction of blast injury from repeated exposures. Again, data collected for other organs, in particular the upper respiratory tract, show that injury occurs at decreasing levels of exposure as the number of exposures increases. The relation in not linear, however, and it is not known if there is a level of exposure for which no injury occurs no matter how many exposures are made. It is also not known how to account for repeated exposures of various intensities. Since the phenomenon is not additive, a better predictive scheme is required.

A final need for a more complete injury prediction involves the factor of safety in protection standards. As the data in Fig 1[1] show, there are combinations of environmental parameters for which the resulting injury can vary dramatically for slight changes in conditions. Confidence in distinguishing hazardous conditions in these regions is greatly diminished and must be reflected in a conservative factor of safety. On the other hand, that margin cannot be applied everywhere without producing overly restrictive regulations.

Sources of Uncertainty in Physical Testing. One means for improving the predictive capability of DRC based on animal tests would be to increase the number of tests to address all of the parameters and needs of interest. There are certain limitations inherent in this approach that are discussed below.

The foremost uncertainty lies in the translation of results between species. The size and material properties of the external ear, canal, and tympanic membrane vary considerably. The orientation and dimensions of the animal place it in positions relative to the blast that differ significantly from that of humans.

Another uncertainty arises from the extrapolation of results. In low-level noise exposures, additive concepts can be used to estimate conditions that are composites of previously studied ones. For the intense circumstances of blast injury, the nonlinear aspects of the phenomenon bring this approach into question. Nonlinearities arise from a variety of sources: the reflection and refraction of shock waves within the ear canal and at the membrane, the inherently nonlinear actions of the ossicles that transmit motion to the inner ear, the finite deformations of the membrane that change its geometry, and the nonlinear material properties of the membrane as it stretches beyond its elastic limit and as it reaches the point of partial failure.

Finally, there is uncertainty associated with the statistics of a limited number of tests. Human tests must be restricted to levels at which no injury occurs, while human exposures under accidental conditions are few in number and the blast conditions are known only approximately. Animals, on the other hand, can be exposed to more energetic conditions, but the large number of possible combinations of pressure fields and repetitions of interest prevents an exhaustive study.

Model Development Program. The sheer magnitude of the number of tests that must be conducted to cover the situations of interest even once, let alone with sufficient statistics, is overwhelming. The cost in resources, time, and animals prohibits such a direct approach. With a more fundamental understanding of the underlying processes, however, it would be possible to minimize the number of tests required and add confidence to the extrapolation of results to humans. Furthermore, a better understanding can guide the development of protective clothing and training doctrine.

The approach that has been taken in the Walter Reed Army Institute of Research blast overpressure modeling program is to use the principles of engineering to develop mathematic models of the processes that lead to injury. The steps in this bioengineering method can be summarized as follows:

1. Divide the phenomenon into its causal parts.
2. Use laws of mechanics to establish quantitative relations.
3. Use laboratory testing to determine material properties.
4. Validate predictions against actual observations.
5. Use the tested model to extend the animal data.

No matter which organ system is considered, the blast injury process can be divided into the following distinct parts. The source of the blast and the geometry of the surroundings combine to produce a pressure load distribution on the body. This loading sets the body in motion and causes distortion of the compliant, air-containing organs. The distortions (strains) of the organ result in forces within the tissue (stresses) that are concentrated at support and special geometric locations. When the stress exceeds the material strength of the tissue, damage is caused that can result in observable injury.

Since the analysis of mechanical systems is a highly developed field, there are many concepts and tools available to the bioengineering approach. Computational gas dynamics and model testing are proven means for predicting the load distribution on an object (the body) under the most general of blast circumstances. Structural analysis, in particular finite element modeling, can describe the distortions and stresses within a structure, taking into account varying geometries and material properties. The study of the failure of structures has produced laws governing material strength and techniques for its measurement.

Conceptually, it should be possible to measure all of the required material properties, construct a finite element model of the entire animal, and then calculate the occurrence of injury. While analysis like this may be feasible for a building or an airplane, the biologic system is far too complex and variable for the approach to be applied strictly. Furthermore, the injury process occurs in composite materials whose modes of failure are not yet known.

Nonetheless, the principles are valid and the laws of mechanics, where they can be applied, are rigorous. The challenge is, therefore, to develop a less complex, but physiologically sound, representation that can be analyzed.

The bioengineering approach described above is being applied currently to other organ systems to provide predictions of blast injury. The upper respiratory tract has the most complete data base of injury for single and repeated exposure conditions. A dynamic model describing the distortion of the trachea under blast loading has been used to produce DRC for injury that include multiple exposure effects and degrees of injury.[2]

Modeling the dynamics of the thorax and lung has required more research effort. Fundamental experiments have been conducted to determine the material properties of lung tissue under static and dynamic conditions.[3] This effort has led to a mechanistic description of pressure waves within the lung parenchyma that can amplify the external pressure loading and result in damage at particular locations within the lung. Field tests have provided direct measurement of these waves and the associated chest wall motions that are being used to validate a structural model of the thorax.[4] It is not yet possible to make DRC predictions, but the reasons for the injury patterns and locations have been identified.

Modeling of the abdominal cavity and injury to the gastrointestinal tract is in a more tentative stage. The bioengineering approach has produced direct evidence, however, of the connection between gas bubbles and injury. Surgical techniques have been developed that allow instrumentation to be placed at precise locations within the gastrointestinal tract while maintaining a viable preparation.[5] Surrogate testing and mathematic modeling has produced a tentative relation between abdominal pressures caused by the blast and the bubble dynamics that cause stress in the tract walls. Here, too, field testing is providing data on in vivo dynamics.

Purpose of Paper. The purpose of this paper is to present an approach to modeling tympanic membrane rupture based on the bioengineering methodology. First, the physical aspects of the biologic system will be identified that are likely to be important to the mechanical aspects of injury. Previous work that provides a starting point will be summarized. Next, a preliminary model of the process is presented. The model is incomplete and simplifies the phenomena involved, but it offers a concrete example of the direction and nature of the results possible from such an effort. A comparison with existing injury data is made. Finally, areas are identified for further research that will remove the simplifications and produce a tool for extrapolating field tests.

MODELING CONSIDERATIONS

Description of Environment. The mechanical process begins with the blast itself, which produces a pressure time history in the location of interest. This pressure is the environment for which one wants to determine potential hazard.

The blast resulting from a single spherical charge in the presence of a flat ground plane has been studied extensively. The characteristics of the blast at a particular location depend upon the energy released by the explosive, the distance from the point of interest, and the height of the explosion above the ground. Depending on these parameters, waves arriving at a particular location could consist of the blast wave from the explosive, a reflected wave from the ground, or a new wave formed from the other two that moves parallel to the ground (the Mach wave). Empiric formulas describing each type have been compiled.[6-8]

When the explosion takes place with other reflecting surfaces present, especially those within enclosures, the reflections and recombinations can become extremely complicated and cannot be described with simple empiric formulas. Even the direction of the wave, which is important to interpreting the output of instrumentation, becomes complex.

Load on Tympanic Membrane. Once the environment has been defined, the load on the tympanic membrane must be determined. As in other auditory studies, it is known that orientation to the source is critical.[9,10] Generally, having the ear normal to the blast will produce the greatest load. For complex waves, the condition of being "normal" is not clearly defined, so that the worst-case orientation may be more difficult to determine.

The pressure wave changes as it passes down the ear canal because of reflections and refractions. The details of the wave motion are complicated, but there is experimental and theoretic evidence that, depending on the length of the canal, the pressure signal can be amplified.[11,12] Most of these results apply to sound waves, so that the corresponding effect on blast waves in the ear is not known.

Once the pressure reaches the tympanic membrane, it will be amplified by reflection. The truncated cone shape of the membrane, however, will change the usual relation between the incident and reflected pressures.

Finally, the use of ear protectors, muffs and plugs, changes the transmission of the pressure wave from the environment to the drum. Again, the reduction in transmission for sound waves has been well studied, but the effect on blast waves is not well known.

Structural Response of Membrane. Once the loading has been characterized, the model must predict the structural response of the membrane. Funnell[13] and Funnell and Laszlo[14] have taken the first step in using finite element analysis to determine the deformation of the membrane. They have used thin plate concepts to study the small deformation of the membrane under loading characteristic of sound waves. The qualitative agreement with experimental observation of vibration patterns in cats shows that the approach is feasible. The following characteristics are important to such analyses.

The pars tensa is an elastic membrane, about 40 μm thick, attached at the elliptical tympanic ring along its outer edge and to the manubrium in the middle.[15,16] Under physiologic conditions it is deformed into a three-dimensional curvature that controls its mode shapes and frequencies of vibration.

The elastic properties of the membrane have been reported by Yamada,[17] Elner et al,[18] and Funnell and Laszlo.[19] Typical values are Young's modulus = $200 \cdot 10^8$ dyne/cm^2; Poisson's ratio = 0.3; mass density = 1.0 g/cm^3.

The variability of these properties among species and under large, rapid deformation is not known.

The nature of the support of the membrane at the ring and the manubrium is critical to predicting stress. A fold of the membrane changes both the magnitude and direction of the stress under loading.

Finally, the mechanical linkage of the ossicles must be part of the structural modeling. The ossicles are designed to protect the cochlea from large amplitude motion of the eardrum and so play a crucial role in the dynamics of the drum at blast level loading.[20-22]

Failure Modes. The final part of the predictive process is to relate stresses that develop in the tympanic membrane in response to damage. The different kinds of injury that have been reported may correspond to different processes.[1] The least damage involves disruption of the tissue and can be related to excessive tensile stress within the body of the membrane. Tears and ruptures at the support locations arise from stress concentration at the connection between the membrane and the ring. It is likely that both the magnitude and direction of the principal stresses are important.

In addition to damage by a single trauma, modeling has to address the damage brought on by repeated exposure. The bioengineering concept of fatigue has proven effective in understanding multiple shot injury to the upper respiratory tract. Fatigue failure is characterized by a lowering of the critical stress of the material under repeated stressing. No measurement of this quantity has been conducted on biologic material.

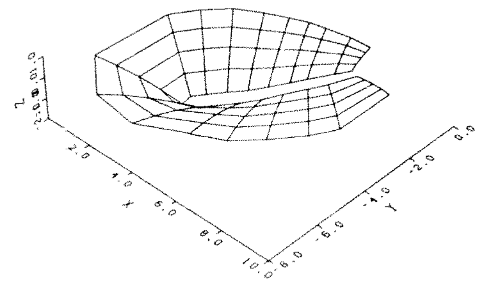
PRELIMINARY MODEL

Although many critical parameters of the biologic system are not sufficiently known at this time, it is illustrative to examine how applicable the bioengineering approach is to the prediction of tympanic membrane rupture. This section provides a preliminary assemblage of models to connect loading at the membrane with observed injury.

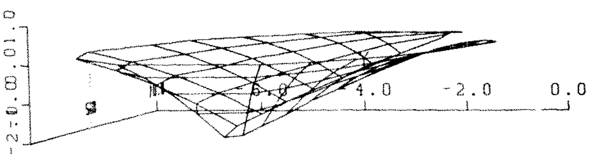
Structural Representation. A mechanical stress analysis was undertaken to gain insight into the process by which pressure loads at the surface of the membrane are translated into the tensile stresses responsible for injury within the membrane. The work follows that of Funnell[13] and Funnell and Laszlo[14] in examining the deflection of the cat eardrum. The analysis was performed by Dr Paul Mlakar of JAYCOR using the Automated Dynamic Incremental Nonlinear Analysis (ADINA) computer program for finite element analyses.

The discretization of the tympanic membrane is shown in Fig 2. The pars tensa is modeled with 68 two-dimensional, four-node, plane stress, quadrilateral elements. The stiffer manubrium and annular ligament are represented by rigid links to the short process of the malleus. The stiffness of the ossicular hinge is represented by a truss element attached to this location. The pars flaccida is excluded from this model. The conical depth and drum curvature are approximated as described by Funnell and Laszlo.[14] The membrane is fixed along the outer tympanic ring, and elsewhere only translations perpendicular to the plane of the ring are considered.

The material properties of the membrane were taken to be those listed earlier. The length, area, and modulus of the truss element were chosen to represent an ossicular stiffness of 1,800 dyne/mm



Top View



Side View

Fig 2. Three-dimensional grid formed by finite elements used to model tympanic membrane. Membrane is considered to be linear, elastic material rigidly attached to tympanic ring and manubrium (not shown).

about an axis 1.7 mm from the attachment point of the manubrium.

The loading was taken to be a uniform, static pressure applied normal to the membrane. The magnitude was 0.2828 dyne/mm², as in Funnell and Laszlo.[14] The response was determined on the assumption that the material was linear and elastic.

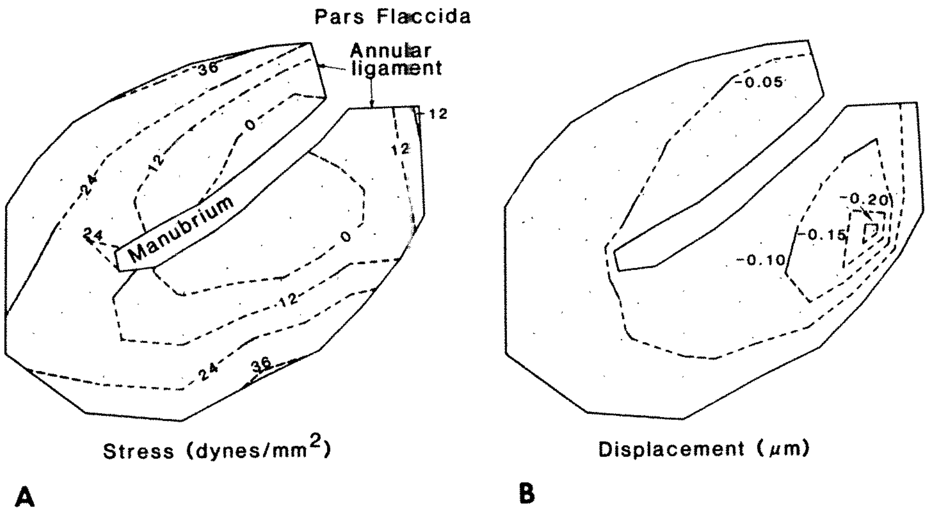
The calculated displacement of the eardrum is shown in Fig 3. The dashed lines represent isodisplacement contours, labeled in micrometers. They indicate that the displacements in the pars tensa exceed those of the manubrium and that the maximum displacement occurs in the posterosuperior region. [—*Editor's note:* The common occurrence of blast perforations in this region (eg, slap injuries to the ear, and water surface perforations resulting from waterskiing) validates this finding. - Brian F. McCabe, MD, Editor, *Ann Otol Rhinol Laryngol*—] The displacement of the manubrium is 0.05 μm, while the maximum in the pars tensa is 0.23 μm. These results compare favorably with those obtained earlier by Funnell and Laszlo.[14]

The calculated stress distribution is shown in Fig 3. The dashed lines represent isostress contours, labeled in dyne/mm². Stress concentrations can be seen at the attachment to the tympanic ring of magnitude 38 dyne/mm² and at the tip of the manubrium of 28 dyne/mm². The average stress within the pars tensa is about 12 dyne/mm².

The variation of stress with applied load is shown in Fig 4. These results have been obtained within the linear regime of the material, but they indicate how different kinds of injury can occur at different load levels. The disruption of tissue structure occurs within the pars tensa and requires a moderate level of tensile stress. When that critical stress is determined, one could determine the critical static load from the response curve for the pars tensa. Tearing of the membrane from the ring, on the other hand, requires a much larger tensile stress. Again, when that stress is known, the critical load can be determined from the response curve associated with the tympanic ring.

As the external load is increased, stress builds up in different parts of the membrane. The critical stress for tissue disruption will be met at one pressure level and that of rupture at another, thereby producing different injury thresholds. The relation between those thresholds depends on the geometry and material properties (which could vary from species to species) and upon the nature of the loading (which could vary from one blast wave to another). What may appear empirically to be a complex relation might be understood readily from a mechanical stress point of view.

Single Mode Dynamic Response. The ADINA computer program is capable of analyzing the motion of the membrane under the dynamic loading of a blast signal, and the program has been used in that way for the response of the thorax to blast load.



Stress (dynes/mm^2)

Displacement (μm)

Fig 3. Static response of tympanic membrane to uniform pressure loading of 28.28 dyne/cm². A) Tensile stress contours, which are concentrated along tympanic ring and at tip of manubrium. B) Displacement contours, which are greatest in posterior region.

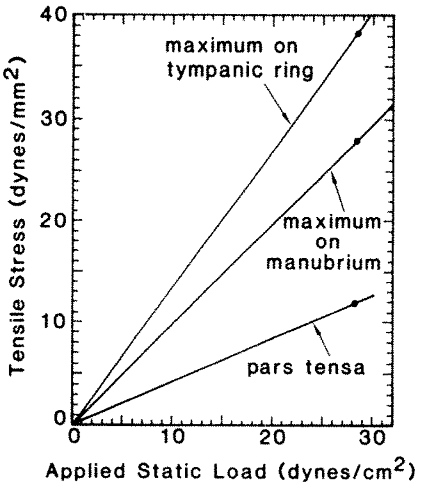


Fig 4. Tensile stress response for various sections of tympanic membrane under uniform pressure loading. Injury is associated with stress exceeding tissue material strength, and so levels of applied pressure at which internal tissue disruption and membrane rupture occur can vary among species.

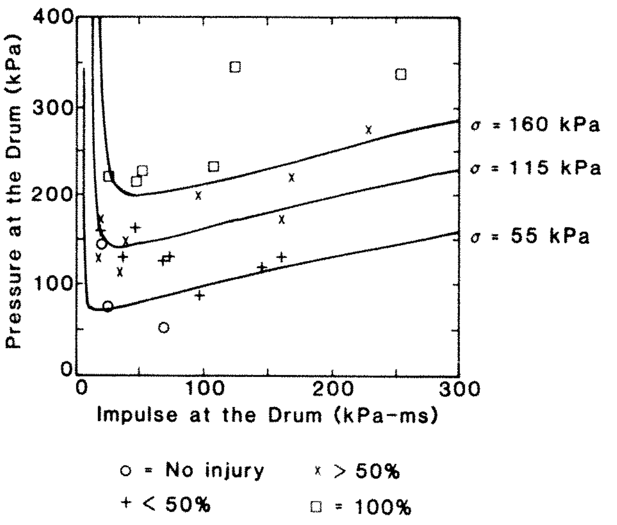


Fig 5. Model prediction of conditions of tympanic membrane rupture. Single mode, dynamic model was used to determine contours of resulting elastic stress. Variation in population critical stress levels is conjectured to be responsible for individual variations in injury.

In this paper, a more elementary analysis will be made on the basis of an assumption of linearity.

When the mechanical system is displaced within its linear range, the motion can be decomposed into modes, each of which can be analyzed separately. The equation describing any particular mode is of the form

$$mx'' + 2(m/t_d)x' + kx = P(t) \qquad (1)$$

where m = mass of the membrane/area, t_d = damping time constant, and k = elastic constant/area.

The elastic constant is determined by the characteristic frequency of the mode being analyzed.

$$f = 2\pi(k/m)^{1/2} \qquad (2)$$

The relation between the environmental pressure field and the pressure loading on the membrane is not completely known. The most complete tabulation of tympanic membrane rupture data,[1] however, is expressed in terms of the membrane load, so for the purposes of comparison, we will take the load as known. It must be kept in mind that the final form of DRC must be in terms of the environmental conditions. The Friedlander representation will be used

$$P(t) = P_m(1 - t/t_o)\exp(-bt/t_o) \qquad (3)$$

where P_m is the peak pressure observed, and t_o is chosen so that the positive duration is matched. In the following analysis a constant value of b = 4 will be used; more elaborate representations are possible.

The equations above can be solved to give the displacement of that mode as a function of time

$$X(T) = (A - BT)\exp(-bT) + [C\sin(\Omega T) + D\cos(\Omega T)]\exp(-\alpha T) \qquad (4)$$

where the dimensionless variables are $x = (P/m)t_o^2 \cdot X(T)$ and $T = t/t_d$, and the solution coefficients are expressed in terms of the parameters $\alpha = t_o/t_d$, $\beta = ft_o/(2\pi)$, $\Omega^2 = \beta^2 - \alpha^2$, $B = 1/(b^2 + \beta^2 - 2b\alpha)$, $A = B[1 - 2B(b - \alpha)]$, $C = [B + A(b - \alpha)]/\Omega$, and $D = -A$.

The assumption of linearity also allows us to assume that the elastic stress, kx, is proportional to the tissue stress in the membrane. From the solution above, we can calculate the elastic stress

$$(\sigma/P)^2 = \beta^2[(dX/dT)^2 + \beta^2X^2] \qquad (5)$$

In particular, we can produce contours of maximum tissue stress in the coordinates of peak pressure and positive impulse. The result is the predicted DRC.

Comparison With Data. If the test population has a variation among individuals that leads to a variation in the critical stress for rupture, then different levels of stress will produce different percentages of injury. There will be a minimum stress below which no individual will suffer injury and a maximum stress above which all will be damaged.

Figure 5 overlays contours of maximum stress, developed in the single mode dynamic model, on the data for observed injury reported by James et al.[1] We have chosen the model parameters to be f = 1.4 kHz and t_d = 10 ms.

A reasonable correlation is produced when 55 kPa and 160 kPa are used as the critical stress extrema for the population.

Other features of the data are also qualitatively reproduced by these results. The trend for injury to occur at larger pressures for larger impulses is a direct result of the membrane damping. While that value is unsubstantiated by measurement at this time, the trend clearly holds for each segment of the population.

The contour lines are very closely spaced at small impulse values and rise sharply to form a lower limit on injury. The observations show a similar behavior in this region. Faired curves through the low impulse data have an apparent steep rise, and the difference in load parameters causing no injury from those causing more than 50% injury is virtually indistinguishable.

AREAS FOR ADDITIONAL RESEARCH

The preliminary results of applying the bioengineering methodology to predicting injury to the ear show several of the important features seen in the data. The model is not yet suitable for constructing DRC, however, until four areas of uncertainty are removed.

Load Definition. Damage Risk Criteria must be expressed in terms of environmental conditions, so that the relation of the external pressure field to the load at the tympanic membrane must be quantified and incorporated into the model. The two primary processes affecting this relation are the gas dynamics along the ear canal and the shock reflection at the curved membrane. Definition of orientation effects in a complex wave environment is an additional consideration.

Structural Model. Although the simple, linear model contained trends seen in the data, the tympanic system has undoubtedly been driven to its nonlinear limits by the large amplitude loading. Therefore, incorporating changes in material characteristics and in the geometry of the membrane will be important to obtaining the correct magnitude of displacement. It is also possible that the material properties are dependent on the rate of stress application. These properties must be determined through direct laboratory measurement.

In the linear model it was assumed that the tissue stress was a constant multiple of the elastic stress due to displacement. For large amplitude motions, the ossicles themselves respond in a nonlinear manner that will change this relationship. Even more important, the stress concentration at the tympanic ring, which is responsible for the rupture of the drum, is not well enough defined to predict the magnitude of stress concentration.

Injury Process. For the sake of illustration, critical stress levels were chosen that captured the boundaries of the data. While this selection would be sufficient to correlate one set of conditions, it could not be used to extrapolate predictions to other species, whose material properties may be different. Furthermore, a more precise definition of injury must be given so that their relation to local stresses can be made.

To be able to make predictions in repeated exposure circumstances, it is necessary to determine the fatigue characteristics of the injury process. Controlled, cyclic stressing of the membrane will produce the desired relations, which should be confirmed by multiple exposures applied in the field.

Validity. The strength of the bioengineering method is not only that the relations are based in the law of mechanics, but that each step in the process can be confirmed separately. Experimental data already exist that would confirm the predicted drum dynamics for small amplitude pressure disturbances, and the same techniques could be applied for blast level exposures.[23-25] This comparison would validate the finite element modeling.

Once the loading, structural response and injury-stress relation have been validated separately, the complete model should be validated against a wide variety of environmental conditions and repeated exposures. Then, the method can be confidently used to extrapolate results to new environments and to guide the development of protective gear and training doctrine.

SUMMARY

The following points summarize the evaluation of modeling in predicting injury to the ear.

1. There are several areas in which the prediction of blast-caused injuries to the ear must be extended.
2. Those extensions can be practically achieved only with a greater understanding of the underlying mechanical processes.
3. The bioengineering approach to modeling blast injury provides an encouraging first step in this direction.
4. That approach identifies a systematic application of mathematic modeling and laboratory testing that can guide and extend animal studies in the field.

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VASCULAR DIZZINESS AND TRANSCRANIAL DOPPLER ULTRASONOGRAPHY

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Dizziness as defined herein will include an illusion of motion caused by various degrees of ischemia to the vestibular pathway or its interconnecting pathways. "Syndrome," such as the lateral medullary syndrome, denotes a macroinfarct, while a microinfarct or an area of incomplete infarct (where there may develop an incomplete degeneration of the neural tissue secondary to the arteriolar microatheromatous stenosis) may cause only one neurologic deficit, such as dizziness per se as the only symptom. However, the latter may presage a larger and more debilitating neurologic deficit. The transcranial Doppler, used to track sequentially the larger basal arteries of the brain, specifically the vertebrobasilar arterial system, is an addition to noninvasive diagnostic methods of separating vascular problems from other causes of dizziness.

KEY WORDS — dizziness, Doppler ultrasonography, vascular system, vertebrobasilar artery insufficiency.

ABBREVIATIONS — ACA - anterior cerebral artery, AICA - anterior inferior cerebellar artery, BA - basilar artery, ICA - internal carotid artery, MCA - middle cerebral artery, PCA - posterior cerebral artery, PICA - posterior inferior cerebellar artery, SCA - subclavian artery, TCD - transcranial Doppler, VA - vertebral artery.

INTRODUCTION

The cardinal symptom in vertebrobasilar arterial insufficiency is dizziness.[1-3] Most otologists have been ingrained with the concept that vertigo must imply an illusion of motion, with dizziness being a separate entity. That is, vertigo is an abnormality in the vestibular pathway and dizziness implies other central nuclei and pathways.

The percept of touch may be sensed as an itch or even pain, depending on the intensity of the stimulus. In the same way, if a stimulus to the vestibular nuclei and/or pathways is minimal, the sensation may not be an illusion of motion, but rather a feeling of being drunk, light-headed, or unsteady. Hence, depending on the intensity of the stimulus to the vestibular nuclei or their pathways, an illusion of motion may not be used in the patient's description. "Dizziness" should encompass many varieties, to include ultimately an illusion of motion or vertigo per se. The usual descriptions of dizziness with occlusion of the vertebral artery (VA) include a feeling of swaying, falling, being "seasick," "being off balance," frank whirling, and rotational turning.[4] When the brain stem reticular formation becomes ischemic, either the ascending reticular activating system or the descending reticular spinal motor system can be affected. Thus, subnormal levels of consciousness may result, or the resultant abnormal facilitory-inhibitory control over limb musculature may cause dysequilibrium. Vascular compromise of one interconnecting system may necessarily affect the other. Again, if the reticular formation in the brain stem becomes ischemic, input from the reticular formation into the vestibular nuclei, or vice versa, may be affected and cause altered vestibular responses. Herein, "dizziness" will include feeling intoxicated, light-headed, unsure of balance, like blacking out, etc, and true vertigo.

VESTIBULAR PATHWAY

The peripheral vestibular pathway includes the membranous labyrinth and the afferent superior and inferior vestibular nerves terminating in the central pathways of the four vestibular nuclei and cerebellum. The vestibular nuclei are located in the medulla and pons (Fig 1). If size of structure is meaningful with regard to importance of function, it is noteworthy that the vestibular nuclei comprise one of the larger nuclear groups in the brain stem. The pons and medulla measure 55 mm in length, while the vestibular nuclei straddling the pontomedullary junction measure 18 mm, or roughly one third of the length of these two structures. The inferior aspects of the medial and inferior vestibular nuclei are located in the rostral medulla, while the superior and lateral vestibular nuclei reside in the caudal pons. The nuclei straddle the pontomedullary junction. It is important to remember that there is a direct central connection from the peripheral labyrinth directly to the cerebellum bypassing the vestibular nuclei. These fibers, as well as fibers from the vestibular nuclei, ascend as the vestibulocerebellar pathway in the restiform body, terminating in the flocculonodular lobe of the archicerebellum. Likewise, cerebellovestibular fibers are efferent to the vestibular nuclei. The brain stem reticular formation contributes important input to the vestibular nuclei and vice versa. Fibers leaving

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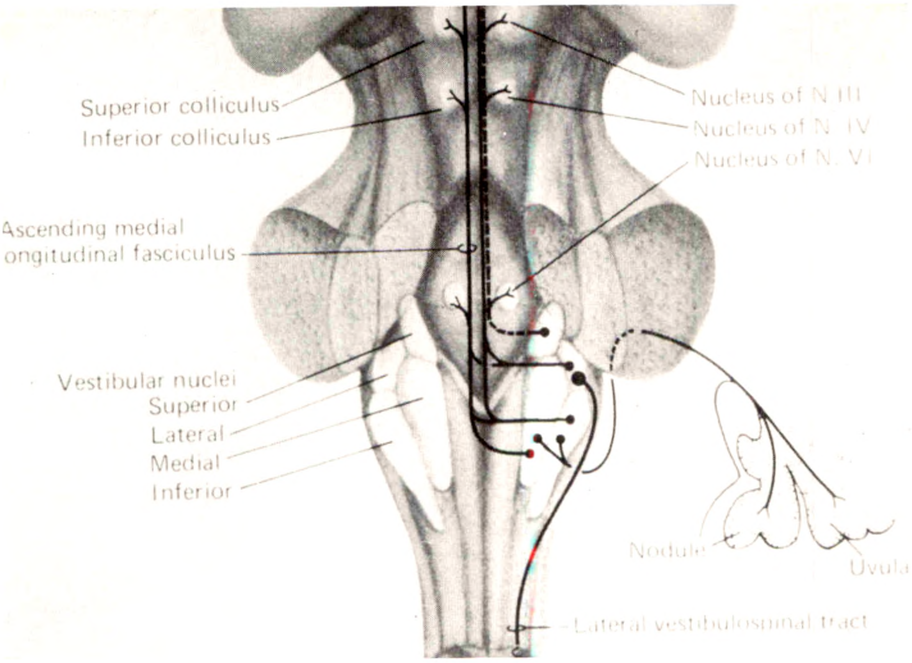


Fig 1. Central connections of vestibular nuclei. Reproduced with permission from Kelly JP. Vestibular system. In: Kandel ER, Schwartz JH, eds. *Principles of Neural Science*. New York: Elsevier Publishing Co, Inc, 1981:417.

the vestibular nuclei ascend in the medial longitudinal fasciculus for reflex extraocular muscle control, while others descend as the lateral and medial vestibulospinal tracts. The vestibular pathway projects superiorly to the thalamus and specifically the ventral posterointermediate nucleus, to terminate in the vestibular area in the parietal lobe. Injury to the above-described pathways by any noxious agent, including ischemia, infarct, or hemorrhage, can cause dizziness.

PRACTICAL ANATOMY OF BRAIN STEM ARTERIAL CIRCULATION

The prime source of ischemia to the above pathways is by way of the vertebrobasilar arterial circulation, which perfuses the brain stem and cerebellum, the posterior circulation. The internal carotid artery (ICA) supplies the cerebrum above the tentorium cerebelli, the anterior circulation.

Vertebral Artery. The clinical significance of ischemia caused by the VA requires a more lengthy discussion of the applied anatomy of this artery (Fig 2). The VA arises as the first branch of the subclavian artery (SCA) and usually enters the transverse foramen of C-6 and rarely of C-5. This is the first (prevertebral) segment. The second (cervical) segment is the interosseous segment within the transverse foramina from C-6 to the atlas. The VA ascends in front of the anterior primary rami of the lower seven cervical nerves and is surrounded by the vertebral venus plexus. Because the atlas (atlantal) supports the skull, it was named after the titan, Atlas, who, according to Greek mythology, supported the earth on his shoulders. After a rather straight vertical ascent, the artery takes a pronounced posterior and lateral ascent from the transverse foramen of the axis. At this juncture it makes a sharp medial turn onto the posterior superior surface of the lateral mass of C-1. The vessel is usually inferior and posteromedial to the tip of the mastoid process. The VA continues on to the sulcus of the VA on the superior surface of the posterior arch of C-1 between the atlas and the occiput. This third (atlantic) segment, after it exits from the transverse foramen of the atlas, passes through the suboccipital triangle roofed by the semispinalis capitis muscle. The floor of the suboccipital triangle consists of the posterior arch of the atlas and the posterior atlanto-occipital membrane. This tortuous segment of the vessel from C-2 to the posterior arch of C-1 apparently thus permits the rotation of the atlas on the axis as well as a variety of head movements. However, this third segment is vulnerable to excessive head manipulation, as will be described later. The fourth intracranial segment already has pierced the dura mater to enter into the subarachnoid space at the cerebellomedullary cistern at the level of the foramen magnum. The intracranial segment is the thinnest part of the VA. There is a marked thinning of the adventitia and media layers, with a reduction in elastic fibers in the media and external elastic lamina.[5] The two VAs uniquely fuse to form one basilar artery (BA).

In one large anatomic study, the two VAs were the same size in 8% of individuals, while in 72% the caliber of one vessel was at least double that of the other, and in certain cases 20 times as large.[6] Thus, it is readily apparent that blood flow constraints of the dominant VA may significantly compromise vertebrobasilar arterial circulation perfusion. In another study, by Fields,[7] in 45% of individuals the left VA is larger, in 25% the right is dominant, and in 21% the sizes are the same. Con-

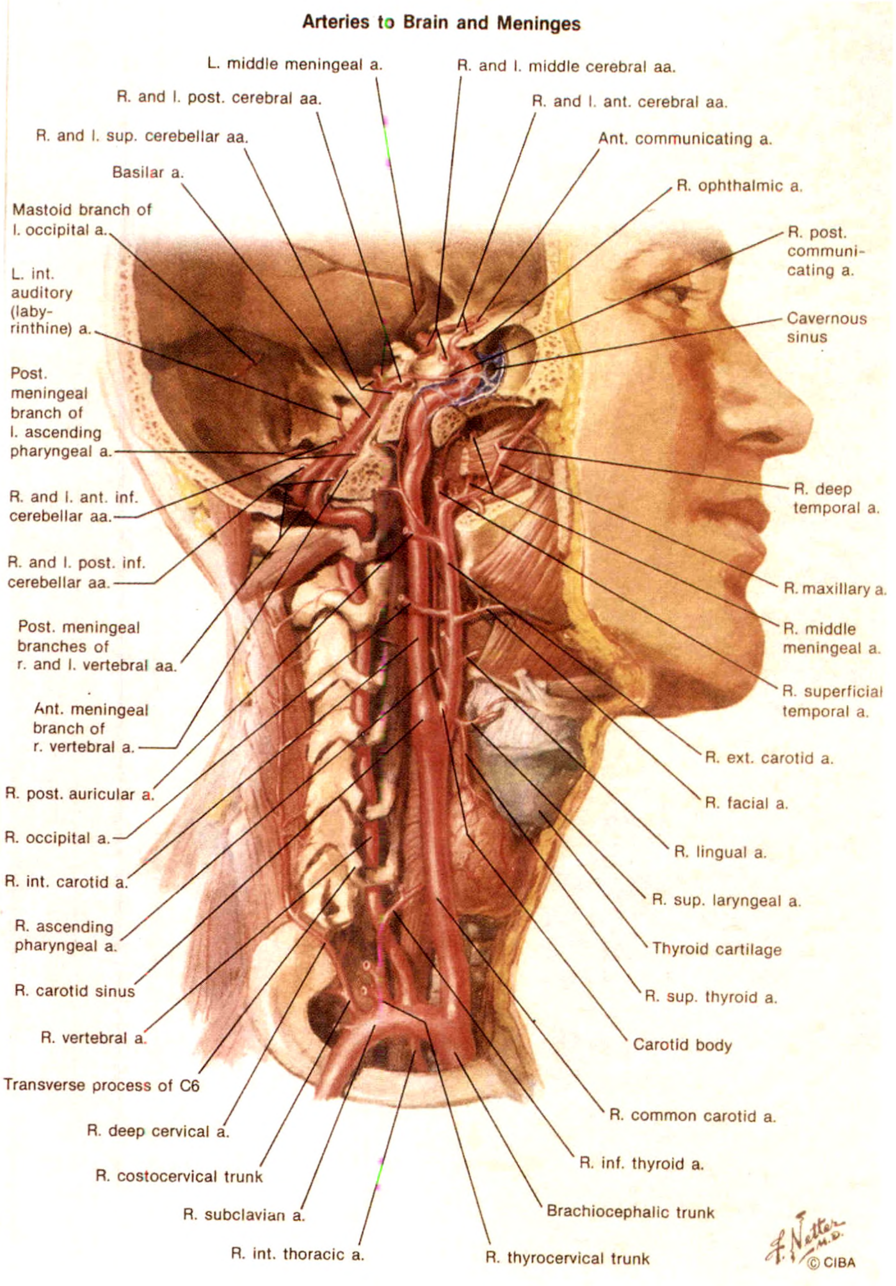


Fig 2. Arteries to brain and meninges. Copyright 1972 CIBA Pharmaceutical Company, Division of CIBA-GEIGY Corporation. Reproduced with permission from *CIBA Collection of Medical Illustrations* by Frank H. Netter, MD. All rights reserved.

trariwise, the common carotid arteries are usually the same size. In 8% of individuals, the left VA does not branch from the SCA, but rather comes directly from the aortic arch.[7] Here, a left SCA critical stenosis, at its origin from the aortic arch or higher and proximal to the usual VA takeoff, would not alter blood flow to the expected VA. An expected possible subclavian steal syndrome would be absent. Also, a transbrachial vertebral arteriogram on this left side would not show any filling of the VA. An arch arteriogram would demonstrate the true origin of the VA. In the subclavian steal syndrome there is a critical stenosis or occlusion of the brachiocephalic artery and/or the SCA proximal to the origin of the VA. Blood is stolen from the vertebrobasilar artery territory to feed the hemic-deprived upper extremity via a retrograde blood flow down the VA to the SCA and finally to the brachial artery. Dizziness of some grade is the most commonly reported neurologic symptom and usually is initiated by arm-hand activity with the vascular-compromised upper extremity. In some patients it is postural, initiated by standing. This is especially true with patients on antihypertensive medication, in whom orthostatic hypotension is a common sequela and thus adds to the already diminished brain stem circulation.

The posterior inferior cerebellar artery (PICA) is the largest branch of the VA, usually arising 1.5 cm inferior to the origin of the BA, but this is highly variable. The PICA on occasion may arise from the

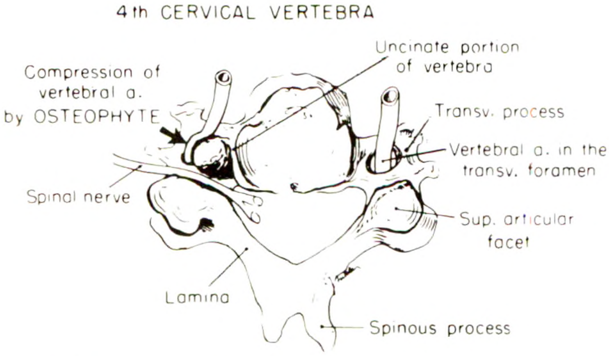

4th CERVICAL VERTEBRA
Uncinate portion of vertebra
Compression of vertebral a. by OSTEOPHYTE
Transv. process
Vertebral a. in the transv. foramen
Spinal nerve
Sup. articular facet
Lamina
Spinous process

Fig 3. Anatomic relation of vertebral artery to vertebrae as shown from above. Arrow indicates osteophyte compressing vertebral artery. Reproduced with permission.[11]

VA 24 mm below the foramen magnum.[8] The VA may terminate in the PICA, also one VA may be vestigial or hypoplastic, in contrast to the larger, dominant opposite VA. Finally, one PICA may be absent.

The PICA and the anterior inferior cerebellar artery (AICA), the latter rising from the BA at the lower border of the pons, are usually reciprocal in size on their corresponding side. A large AICA usually means a small PICA.[4]

The blood supply to the brain stem and cerebellum is by the two VAs and the BA and their branches. The BA usually narrows distally.

Blood flow from the VA can be compromised mechanically as it ascends through the cervical transverse foramina. Deformities of the cervical spine are normal radiographic findings in the elderly. Susse[9] states that radiographically visible cervical morphologic deformities occur in 25% of patients under 40 years of age, in 50% of individuals 40 to 50 years of age, in 70% of individuals 50 to 60 years of age, and lastly in 90% of individuals over 60 years of age. Similar data have been reported by Schoen.[10]

Mechanical compression of the VAs may produce clinical brain stem ischemia symptoms similar to those of arteriosclerotic occlusive disease, but in a much more dramatic fashion. Here again, the most common patient complaint is dizziness (all grades) 75% of the time. Osteophyte formation on the cervical vertebrae is found most commonly at the uncinate portion, which projects medially into the transverse foramen (Fig 3[11]). Thus, an osteophyte here may readily compress the VA (Fig 4[11]). The VA compressed by head turning is usually on the side ipsilateral to the side to which the face is turned. However, there is no consistent general rule: any rather extreme cervical movement to the right or left, hyperextension, hyperflexion, or any combination, may compress the artery, depending on the locus and morphology of the bony deformity. There is also a physiologic contralateral compression at the atlas augmenting the constriction when an osteophyte is present. If the constriction is to the dominant VA and/or if the lumen already is compromised because of atherosclerosis, serious brain stem ischemia may be initiated by head rotation.

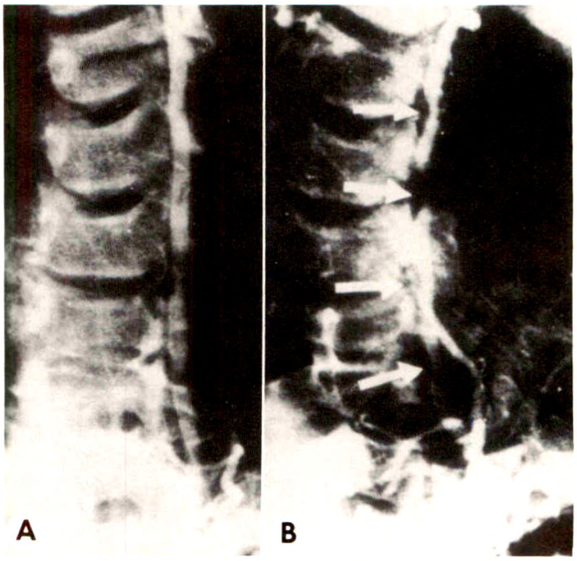


Fig 4. Left transbrachial vertebral arteriogram. A) Left: head is rotated to right. Vertebral artery is normal in this position and with head straight. B) Head is rotated to left. Arrows point to four areas of stenosis when head is in this position. Reproduced with permission.[11]

What if the VA and/or BA craniad in the brain stem already is sustaining an ischemic state because of atherosclerosis? Thus, when the transverse foramen is encroached upon by an osteophyte, an additional cause of diminished blood flow to the brain stem may be initiated by head rotation. This combination of factors may cause significant clinicopathologic hemic disturbances to the brain stem, cerebellum, and even higher centers.

It had been suspected that the posterior circulation could be jeopardized by neck manipulation. In 1947, two cases were reported in which two previously healthy individuals became unconscious after chiropractic neck manipulation and died within 24 hours. In the first case, a 32-year-old man had occlusion of the BA, left PICA, and right AICA, along with brain stem and bilateral cerebellar softening. The second patient was a 35-year-old woman who first complained of feeling dizzy, whereupon the chiropractor carried out further neck manipulation. She subsequently became unconscious and died without regaining consciousness. Necropsy revealed an occluded right VA and BA, as well as an occluded left PICA with the cerebellar tonsils forced into the foramen magnum.[12] Fifty additional reports of posterior circulation stroke ensued after neck rotation or neck injury.[4] These are usually younger healthy individuals whose average age is 37 years. Some other examples included rotating the neck while driving or while actively engaged in archery or yoga, a wife manipulating her husband's neck, and wrestling with neck twisting. All can be and have been devastating in causing brain stem stroke. However, considering all mechanisms of neck twisting with resultant posterior circulation stroke, chiropractic neck manipulation ranks high on the list as the major cause.[4] We must always be mindful of the above, especially in otologic surgery, in which the head has to be rotated, sometimes to the extreme. Any patient, but especially the older patient under general anesthesia, may have the head rotated so as to compromise brain stem circulation. Thus, elderly patients, especially those who are hypertensive with concomitant cervical arthritis and/or those with diabetes, are especially at risk. It is, by far, safer to rotate the operating room table, without excessively twisting the neck, in order to bring the ear into position for surgery. General anesthesia with concomitant use of muscle relaxants reduces the splinting of the cervical vertebrae furnished by the neck musculature. This enhances any combination of rotation, flexion, and extension of the cervical vertebrae, permitting a greater degree of VA compression.

Brain Stem Penetrating Vessels. There are three anatomic groups in the schema of penetrating vessels stemming from the VA and BA: 1) the median arteries, which supply the paramedian basal and tegmental areas; 2) the short lateral circumferential arteries that supply the intermediate basal and tegmental area; and 3) the long lateral circumferential arteries that encircle the brain stem anteriad-posteriad and supply the lateral basal and tegmental regions. The superior cerebellar artery, which arises from the rostral portion of the BA just below the oculomotor nerve, PICA, and AICA, comprises the long lateral circumferential vessels and gives origin to the posterior penetrating branches that supply the lateral tegmentum. The smaller penetrating vessels of the VA and BA are the most uniform in distribution and supply the basal area of the brain stem. There are also medial, lateral, and posterior penetrators. Penetrating vessels are usually less than 200 μm in diameter, and the length of the vessels is proportionate to vessel size. Finally, the medial tegmental region has the best collateral blood supply, in contrast to poorer collaterals in the base or lateral tegmentum. Hence, infarct is more prevalent in the base or lateral tegmental anatomic sites.[4]

Brain Stem Vertebral Artery Branches Pertinent to Dizziness. Branches of the VA that supply the brain stem pertinent to pathways that can cause dizziness include 1) the right and left median perforating branches that penetrate the medulla centrally; 2) the short lateral circumferential branches, including a vestibular nuclei source; and 3) the PICA, which, as the name implies, supplies the posterior-inferior aspect of the cerebellum, including the tonsils, part of the inferior cerebellar peduncle, and the medulla laterally. The PICA takes an extremely sinuous course.

Brain Stem Basilar Artery Branches Pertinent to Dizziness. The BA branches are as follows: 1) the median and circumferential pontine arteries; these supply the pons, inferior part of the midbrain, and the anterior aspect of the cerebellar cortex; 2) the AICA, which supplies the anterior inferior cerebellum, plus the middle cerebellar peduncle, lateral pons, and the medulla containing the vestibular and cochlear nuclei; 3) the labyrinthine artery, which may arise directly from the BA, but more commonly from the AICA; 4) the SCA, which is a branch artery and supplies the superior half of the cerebellum, superior cerebellar peduncle, and posterior aspects of the midbrain; and 5) the BA, which terminates by dividing into right and left posterior cerebral arteries (PCAs) as it winds around the cerebral peduncle just superior to the occulomotor nerve, and these supply the temporal and occipital lobes.[13]

Clinical Pathophysiology. If possible, blood goes where blood is needed and follows the path of least resistance. When there is an occlusion of the larger arteries such as the VA, PICA, AICA, etc, the symptom complex is not consistent because of collaterals and the anatomic vessel variations from patient to patient. However, as previously stated, the smaller penetrating vessels are more uniform. Thus an infarct caused by a penetrating branch occlusion may cause only one specific topographic, clinically symptomatic lesion. Hypothetically, a microinfarct within the vestibular nucleus, restiform body, or any site affecting the ramifications of the vestibular pathway may display clinically as dizziness and only dizziness because of this discrete lesion. The one symptom, dizziness, may presage a major stroke, albeit rarely.

If a dominant VA is occluded, then blood flow to the AICA may be diminished markedly and is dependent on collateral flow and anterior circulation retrograde flow. Because of the diminished pressure head and the constant vicissitudes of blood pressure, both auditory and vestibular fluctuations can occur. Blood flow to the brain stem as well as to the labyrinthine artery can be affected.

Since the penetrating vessels are so small, less than 200 μm, the ischemia to the area develops over hours to days, in lieu of a more protracted period when the VA or BA is occluded.

Microatheroma in a small penetrating arteriole may sufficiently block a microembolus derived from the heart or an extracranial SCA-VA plaquing area. This would initiate a complete lumen occlusion with a localized infarct.

Normally, there exists a steep pressure gradient between the high pressure initiated by the cardiac pump and the progressively diminishing pressure as the blood traverses from the larger size arteries to the smaller arterioles (<500 μm) and then to the smallest capillary. Finally there is a negative pressure in the neck jugular veins. This series of events exists with erect posture and is modified by the diameter and length of the vessel as well as blood viscosity. When there is a reduction of blood pressure or an increase in peripheral resistance, there develops a point of no pressure skewed toward the arterial side of the system. Atherostenosis of the VAs and/or the BA reduces the blood pressure head as well as poststenotic blood flow. This resultant diminution of blood flow shows itself anterograde along the whole vessel and its branches. Thus, symptoms are expressed clinically at a site remote from the original stenosis. The topography of the vestibular nuclei in the rostral part of the posterolateral medulla and pons requires long, thin circumferential vessels originating from the VAs and the BA, respectively, for their vascular profusion needs. This protracted anatomical course makes this vestibular nuclei locale least at the bottom site of the pressure gradient and particularly susceptible to the above-presented hemodynamics. William and Wilson[3] state, "Intermittent vertigo of central origin is the commonest early symptom of the syndrome of basilar artery insufficiency."

In 55 episodes of intermittent neurologic syndromes due to brain stem vertebrobasilar arterial insufficiency in 23 patients, Loeb and Roccatagliatta[14] found that "vertigo" was the most common symptom and occurred in 45.5% of the cases. It frequently was brought on by sudden postural changes. "Vertigo" as an isolated symptom occurred in 10% of the cases. The main symptoms were vertigo, diplopia, photopsia, bilateral and transient blindness, dysarthria, suboccipital headache and vomiting, dysequilibrium, dysphagia, and leg weakness. The signs found on clinical examination by directly observing 50 attacks included ataxia, visual disturbances, seventh nerve paralysis, hemiparesis, paralysis of cranial nerves IX and X, dysarthria, and disturbances of consciousness.[14]

Fisher[2] reported 112 autopsied cases with BA occlusion; 86 of the patients or 77% experienced dizziness. In 25% of the cases, dizziness was the only presenting symptom, ie, hearing loss, tinnitus, diplopia, etc, were absent initially. Thus, the dizziness represented the prodromal transient ischemic attack. However, the dizziness usually was associated with other brain stem symptoms, and in this series was found in 50% of the cases. Lastly, in approximately 25% of the cases, dizziness was not the first symptom. The usual sequence of symptoms associated with dizziness as the initial manifestation were listed in the following order of frequency: diplopia, dysarthria, weakness (unilateral or bilateral), headache, numbness of the face or limbs, ataxia of gait, cerebellar limb ataxia, and lastly visual impairment.

Grad and Baloh[15] recently reported 84 patients who presented with vertigo on a presumed vascular basis. The vertigo always lasted "minutes," which is pertinent. These authors noted a "surprisingly" high incidence of vertigo as a singular presenting symptom. Sixty-two percent of the patients had accompanying brain stem symptoms to conclude vertebrobasilar artery insufficiency as a logical diagnosis. Grad and Baloh found the following symptoms in 42 patients with vertebrobasilar artery insufficiency that may be associated with vertigo: visual dysfunction (diplopia, illusions, hallucinations, field defects, blindness), drop attacks in 29 patients, dysequilibrium in 14 patients, weakness of extremities in nine patients, confusion in nine patients, headache in seven patients, hearing loss in six patients, loss of consciousness in six patients, numbness of extremities in four patients, dysarthria in four patients, tinnitus in four patients, and perioral numbness in two patients. The above group had at least one occasion of vertigo as the sole symptom. However, in 19% the ischemic event presented initially as vertigo; where there was infarction present in the vertebrobasilar perfusion territory, 29% had a minimum of one episode of only vertigo antedating the infarction. These singular vertiginous events rarely persisted longer than a few months. However, in two patients the vertiginous events persisted between 1 and 2 years; in one the accompanying brain stem and cerebellar symptoms developed, and in the second patient a stroke occurred in AICA territory including the labyrinth.

The patients with vertebrobasilar artery insufficiency who have brain stem transient ischemic attacks usually have more events than the patient with carotid attacks. However, with the former the prognosis is better. The subsequent mortality rate was found to be higher with carotid transient ischemic attacks than with vertebrobasilar ones.[16] Wilkinson et al[16] go so far as to recommend that in the elderly any occurrence of nonspecific dizziness, lightheadedness, or loss of balance should be considered as a prodromal manifestation of stroke and require therapy for stroke prevention.

Lipohyalinosis. Arterioles less than 200 μm in diameter, which include the small penetrating branches, can become occluded if they develop lipohyalinosis. Lipohyalinosis is a subintimal hyaline deposit in the wall of penetrating vessels that takes up stains used to identify fat. Lipohyalinosis will reduce or indeed stop blood flow. It causes small lacunes (holes) in brain tissue. Microatheromas in these penetrating vessels are associated with hypertension of long duration, while the next stage is lipohyalinosis. Lastly, fibrinoid necrosis of the vessel wall is found with extremely high blood pressure.[4]

Neuropathologists generally have considered lipohyalinosis as arteriolar sclerosis. Initially, there is atherosclerosis of varying degrees of the primary arterial vessel with subsequent stenosis or occlusion of the perforator artery. The smaller branches of the perforator arteries, the arteriole penetrators, develop the arteriolar sclerosis with microatheromatous stenosis. These arteriolar changes are found predominantly in the hypertensive individual or in some normotensive elderly persons. Diabetes is an added factor enhancing the atherosclerotic arterial degenerative process. The arteriolar smooth muscles degenerate and are replaced by fibrous tissue. Plasma enters via the damaged intima into this replaced fibrous tissue causing a "hyaline" appearance. Consequently, this creates a thickening of the arteriolar wall and the lumen is narrowed or obliterated. Thus, varying degrees of localized ischemia or complete anoxia to the microtissue area can result. There may be a small complete or incomplete infarct. Incomplete degeneration of the myelin sheath and axons can be found in lieu of a distinct focal infarct. The above series of events is present with arteriolar sclerosis of the deep penetrating arteries of the cerebral white matter in Binswanger's disease (progressive subcortical encephalitis). The arterioles demonstrate fibrinous or hyaline thickening and finally a fibrinoid degeneration.[17]

Cerebral Autoregulation Hemodynamics. The terminal vasculature immediately prior to and after the capillary bed behaves in its own characteristic manner. The arterial and venous microvasculatures possess smooth muscles and carry out spontaneous contractility. This behavior differs from that of capillaries, which have no smooth muscles. These terminal vessels are under a different central control than the larger vessels.

The contractility or vasomotion is brought on by alternate contraction and relaxation of the smooth muscles and takes place in arterial, venous, and lymphatic vessels. The intensity of the contraction of the vessel wall may be strong enough to close the lumen, or be so weak as to have no effect on blood flow. Thus, blood flow into the capillaries is affected directly by the terminal arteriolar vessels' degree of, or lack of, vasomotion. This is the purest form of autoregulation.

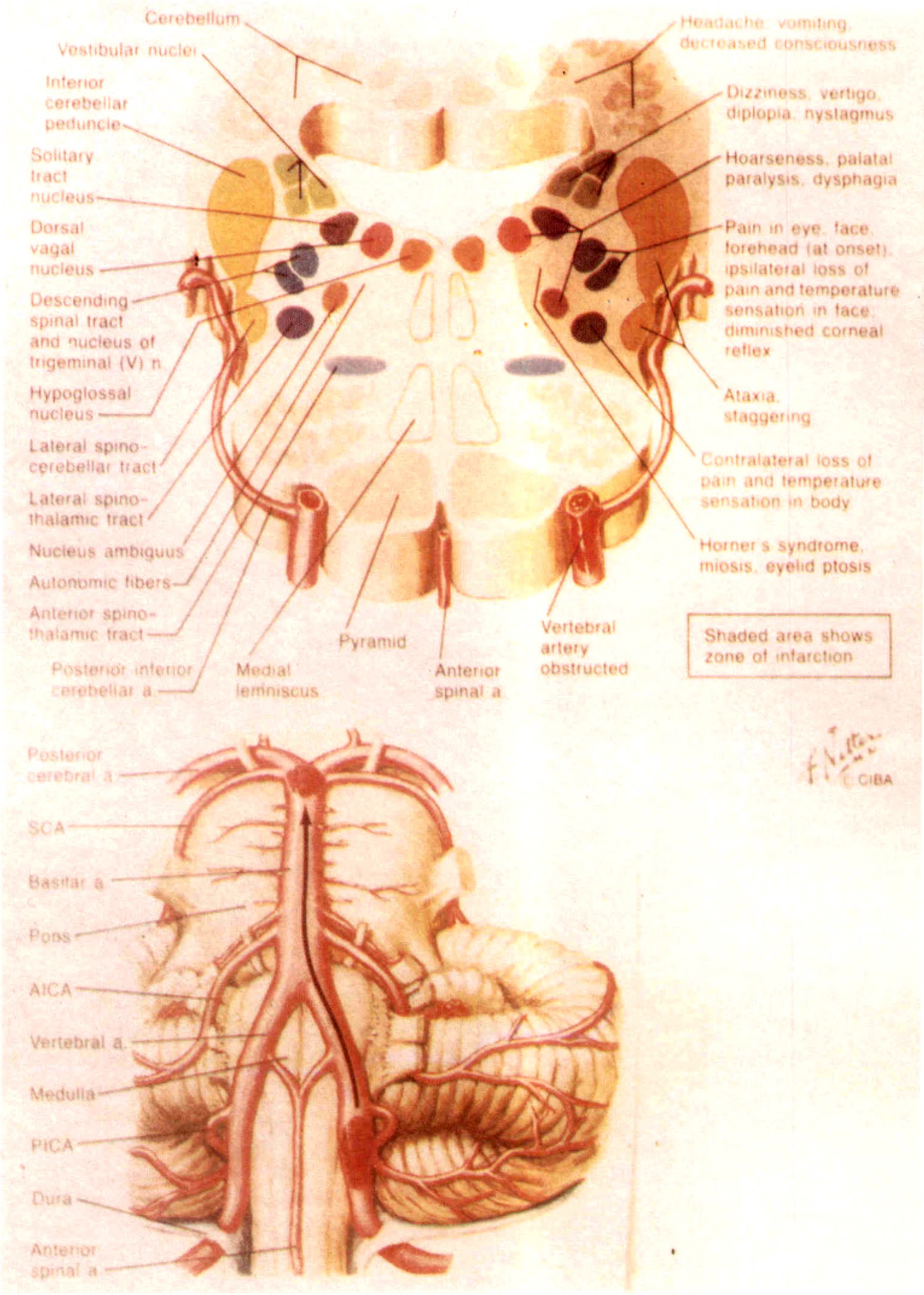
An increase in blood volume to the vessel increases the intraluminal pressure with a subsequent increase in contractility. This stretch response is the myogenic theory of autoregulation. Since blood volume and lumen distention is the dynamic force for vasomotion and subsequent blood flow to the capillary bed, a proximal lack of blood flow in or to the terminal vessels will affect irrigation to the capillary bed accordingly. Atherosclerosis of the penetrating vessels, microemboli, diminished cardiac output, or subintimal thickening by lipohyalinosis all can slow down or indeed prevent contractility, with resultant ischemia to the capillary bed.

It has been shown that these terminal beds are totally independent of the CNS.[18] Surgical or chemical denervation of the bat's wing caused relaxation of the arterial macrocirculation, while the terminal vessels of the arterial system showed increased contractility. Thus, the microvessels were reacting to the lack of control by the larger denervated parent vessels and now were the monitors of peripheral resistance. The terminal vessels continued to control flow into the capillary network distal to the precapillary sphincters.[18]

Factors That Augment Diminished Perfusion and Symptomatology. It is important to be aware that when there is stenosis of a vessel of any size, blood flow can be compromised further by other factors. For example, circulation is most sluggish on rising in the morning or after a nap. It is normal for blood pressure to drop during sleep. An awake blood pressure of 90 over 60 may drop to 60 systolic and 30 diastolic during sleep. Thus, sudden changing from a flat position to a standing position could temporarily initiate symptoms of dizziness because of the orthostatic effect. The blood pressure drop adds to the already curtailed brain stem perfusion. Consider the patient with vertebrobasilar artery plaquing with a resultant diminished blood flow to the brain stem. When this patient rises from bed, the abruptly diminished blood supply to the central vestibular system and/or the labyrinthine artery may initiate dizziness. Here, there are both central and peripheral vascular causes for the dizziness.

Microaneurysms (50 μm) can attenuate perfusion and predominate in hypertensives, especially in those over 65 years of age.[19] Anything that increases blood viscosity will diminish blood flow, eg, macroglobulinemia, hypercoagulability, polycythemia, or sickle cell anemia. Vessel constriction during an attack of brain stem migraine may further compromise the stenotic site. Certain disease processes predispose to intravascular thrombosis: polycythemia rubra vera, thrombotic thrombocytopenia purpura, disseminated lupus, and heavy protein diseases. A high sedimentation rate, usually greater than 50 mm/h, in the patient over 60 years of age may incriminate temporal arteritis with constriction of the vessel lumen. Temporal arteritis is also known as cranial arteritis or giant cell arteritis. The third part of the VA, the infraclinoid siphon, may also be involved in temporal arteritis. The superficial temporal arteries are intensely tender during the acute phase. Blindness, cerebral infarction, deafness, and polymyalgia may occur with temporal arteritis, secondary to the granulomatous arteritis. Embolization because of auricular fibrillation may be a consequence of thyrotoxicosis. Either macroembolization or microembolization may ensue from an acute myocardial infarct.

Glaucoma can be secondary to a critical stenosis in the ipsilateral ICA. The ischemia to the bulb of


Cerebellum
Vestibular nuclei
Inferior cerebellar peduncle
Solitary tract nucleus
Dorsal vagal nucleus
Descending spinal tract and nucleus of trigeminal (V) n
Hypoglossal nucleus
Lateral spino-cerebellar tract
Lateral spino-thalamic tract
Nucleus ambiguus
Autonomic fibers
Anterior spino-thalamic tract
Posterior inferior cerebellar a
Medial lemniscus
Pyramid
Anterior spinal a
Vertebral artery obstructed
Headache, vomiting, decreased consciousness
Dizziness, vertigo, diplopia, nystagmus
Hoarseness, palatal paralysis, dysphagia
Pain in eye, face, forehead (at onset), ipsilateral loss of pain and temperature sensation in face, diminished corneal reflex
Ataxia, staggering
Contralateral loss of pain and temperature sensation in body
Horner's syndrome, miosis, eyelid ptosis
Shaded area shows zone of infarction
F. Netter
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Posterior cerebral a
SCA
Basilar a
Pons
AICA
Vertebral a
Medulla
PICA
Dura
Anterior spinal a

Fig 5. Intracranial occlusion of vertebral artery. Posterolateral medullary infarction and clinical manifestations. Intracranial obstruction of vertebral artery proximal to origin of posterior inferior cerebellar artery may be compensated by preserved flow from contralateral vertebral artery. If posterior inferior cerebellar artery origin is blocked, lateral medullary syndrome (top picture) may result. Clot also may extend to block anterior spinal artery branch, causing hemiplegia, or embolization to basilar bifurcation may cause "top of basilar" syndrome. Copyright 1972 CIBA Pharmaceutical Company, Division of CIBA-GEIGY Corporation. Reproduced with permission from *CIBA Collection of Medical Illustrations* by Frank H. Netter, MD. All rights reserved.

the eye because of the reduced blood flow in the ophthalmic artery may cause neovascular membrane formation, blocking fluid outflow in the globe and resulting in glaucoma.

Almost any variety of dizziness, including an illusion of motion, can be the sole premonitory symptom before the patient develops diplopia, dysarthria, etc. Thus dizziness of itself can antedate a major stroke. If dizziness persists for 6 weeks without any other symptoms, involvement of a large vessel such as the VA or BA is most unlikely (L. R. Caplan, personal communication, 1987). With dizziness as the only presenting symptom, Fisher states that a stroke usually will be declared in less than 6 weeks.[2] However, there may be exceptions to Fisher's dictum.[15,20]

Finally, one must conclude that dizziness on a vascular basis must be considered if the patient (especially the elderly patient) has other cardiovascular infirmities. If there is a history of any one or a combination of the following — previous stroke (especially brain stem), angina, past myocardial infarct, intermittent claudication, hypertension, diabetes, carotid artery and/or SCA bruits — the dizziness should be considered to be of vascular causation until proven otherwise.

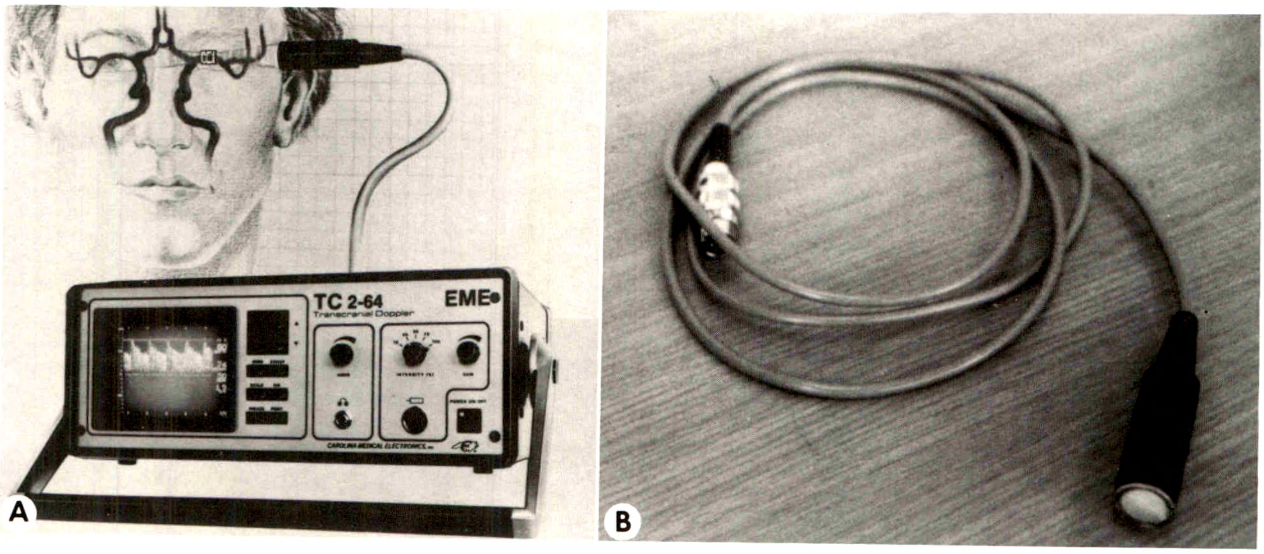


Fig 6. A) Transcranial Doppler, TC 2-64. B) Two-megahertz Doppler probe measures 17 mm in diameter, with length of 50 mm.

LATERAL MEDULLARY SYNDROME

The brain stem area especially important to neurotology is the anatomy surrounding the pontomedullary junction. Ischemia or infarct in this area would include the vestibular nuclei, reticular formation, and restiform body. The lateral medullary syndrome was described initially by Adolf Wallenberg[21] in 1895 and subsequently referred to as the Wallenberg syndrome (see Appendix).

The lateral medullary area can be infarcted variously, causing different patterns of symptoms among patients (Fig 5). Wallenberg attributed the infarct to occlusion of the PICA in the case he reported, but there remains a question mark in the title of his report, "Acute Bulbar Disturbance (Embolus of the Left Posterior Inferior Cerebellar Artery?)."[21] However, Fisher, a pioneer and major contributor to the literature on the pathohemodynamics of cerebrovascular circulation and its sequelae, with his group[22] showed that lateral medullary infarction was due primarily to VA occlusion and/or stenosis. In 16 cases of lateral medullary syndrome, the VA was occluded; in one case it was severely stenotic, and in only two cases was the PICA alone involved. The occlusion is usually from a propagating thrombus arising from an atherosclerotic segment of the VA.[22]

The extent of the infarct to the lateral medulla is variable, depending on the vascular supply routes affected. It usually is a wedge involvement from the inferior olivary nucleus ventrally to the restiform body dorsally, or in some cases further, so as to infarct the cerebellum. Inferiorly, it usually is within the midolive, extending superiorly 10 mm to the pontomedullary junction.[23]

Because of the propensity of dynamic extension of thrombotic occlusions, transient ischemic attacks usually precede the lateral medullary stroke by days, weeks, or possibly months. The following is the symptom complex of lateral medullary syndrome, with dizziness being the most common symptom: 1) dizziness, frank whirling, rotational turning, a feeling of swaying, being seasick, or being off balance (vestibular nuclei and their connections, restiform body, cerebellum); 2) visual disturbances, such as diplopia, blurred vision, or nystagmus (vestibulo-ocular reflex alterations); 3) nausea and vomiting (secondary to vestibular insult, vomiting center in the floor of the fourth ventricle, the parasympathetic dorsal nucleus of the vagus [nerve X]); 4) ipsilateral facial pain, sticky pain in the face or eye, or hypesthesia of the face, supplied by the ophthalmic division of nerve V (nucleus of descending tract of nerve V); 5) occipital headache (descending spinal tract and nucleus of nerve V, or VA dilation); 6) ataxia, disequilibrium or a veering to the ipsilateral hypotonic side of the lesion (restiform body, vestibular nuclei, cerebellum); 7) hiccough (possibly cranial nerve X or respiratory center); 8) dysphagia, hoarseness, and dysarthria (nucleus ambiguus); 9) numbness, burning contralateral extremities or trunk (lateral and ventral spinothalamic tract); 10) ipsilateral Horner's syndrome (sympathetic tract).[4]

MATERIALS AND METHODS

There are many invasive and noninvasive methods for studying cerebrovascular hemodynamics. This paper will be devoted to the use of the noninvasive Doppler and primarily the 2-MHz transcranial Doppler (TCD) (Fig 6A). The TCD used in this study is manufactured by the EME Corporation in the Federal Republic of Germany. It is distributed in the United States by Carolina Medical Electronics, Inc, of King, North Carolina. Many new manufacturers of the TCD have entered the marketplace within the past 2 years.

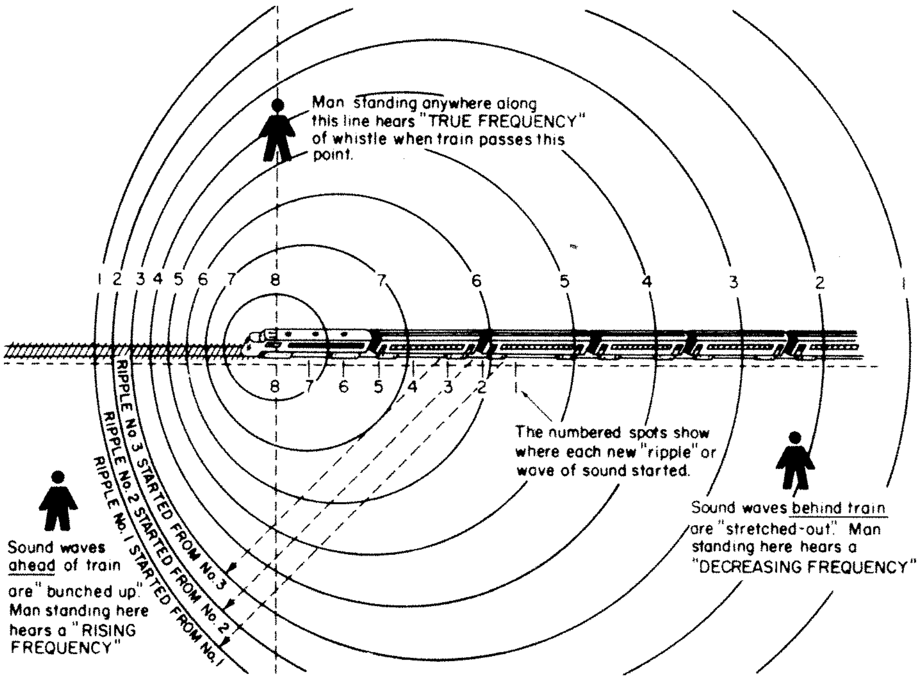
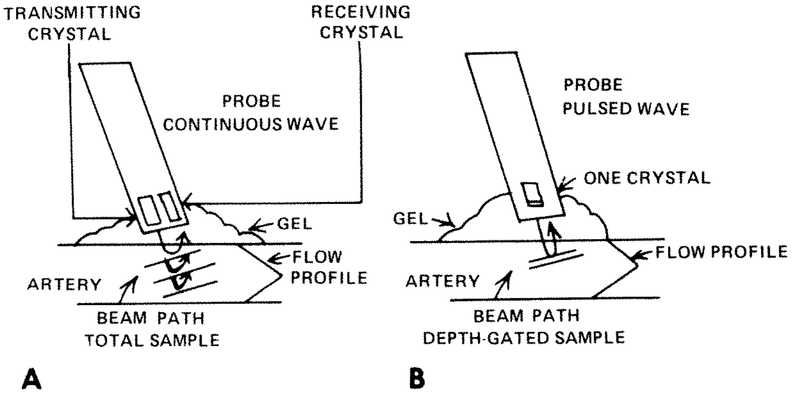

Man standing anywhere along this line hears "TRUE FREQUENCY" of whistle when train passes this point.
1 2 3 4 5 6 7 8
7 6 5 4 3 2 1
8 7 6 5 4 3 2 1
The numbered spots show where each new "ripple" or wave of sound started.
Sound waves behind train are "stretched-out". Man standing here hears a "DECREASING FREQUENCY"
Sound waves ahead of train are "bunched up". Man standing here hears a "RISING FREQUENCY"
RIPPLE No. 3 STARTED FROM No. 3
RIPPLE No. 2 STARTED FROM No. 2
RIPPLE No. 1 STARTED FROM No. 1

Fig 7. Doppler effect, showing how frequency of train whistle is affected as train approaches and recedes from observer. Reproduced with permission from *Basic Principles of Sound. Audio Second Edition Encyclopedia*. Indianapolis: Howard W. Sams & Company, 1969:31.

Historical Background. The Doppler principle was first published in 1843 by the mathematician, physicist, and astronomer Christian Johann Doppler.[24] He studied the relationship of the frequency of a wave to the motion of the source and the observer relative to the medium in which the wave is being propagated. His initial observations were in astronomy. The principle, however, applies to all wave phenomena, and Doppler applied his observations to optics and acoustics. It was Buys Ballot[25] in 1845 who verified the acoustic Doppler effect. Buys Ballot's classic experiment utilized several trumpeters who were placed in a moving locomotive. Essentially, there is an increase in frequency of the pitch as perceived by the stationary observer as the train approaches and a decrease in pitch as the train passes. This pitch variation is a corresponding change over the rest frequency that would be measured if the train was not moving. The Doppler shift refers to the magnitude of the frequency change. Frequencies increase as the frontal sound waves (light waves, radio waves) approach the stationary observer's ear, maximize at the observer, and attenuate and thus have a lower frequency as the source passes the observer. As the train with the trumpeters approaches the observer's ear, the frontal waves are receiving an additive effect with a resultant increase in frequency (Fig 7).

Doppler Probes. Doppler probes utilize ceramic materials that have piezoelectric properties, such as barium titanate (as used with the TCD), which can change shape and yield vibrations when an electric voltage is applied to the crystal, and vice versa. Ultrasound energy is generated by the electrically transduced piezoelectric element. Dopplers can range from 1 MHz to 10 MHz for various uses in medicine. The crystal can send ultrasound as well as receive ultrasound and transduce the latter to an electric signal. The mechanical properties and shape of the crystal controls the natural resonance or ringing frequency; ie, the less thick it is, the higher the frequency of the sound wave emitted. There are a variety of vibration modes used to trans-

Fig 8. A) Continuous wave Doppler: two crystals, one to send and one to receive simultaneously; entire vessel sampled. B) Pulsed Doppler: one crystal alternately pulsed to send and then receive; vessel sample depth-controlled, range-gated.



mit ultrasound, and the choice is dependent upon length, thickness, disc shape, or radial mode when each is polarized similarly. The thickness or compression mode is used most frequently in ultrasonic instruments. Basically, there are continuous wave Doppler machines that continuously transmit and receive ultrasound waves using two separate transducers, one to send and one to receive, simultaneously. Here, a frequency shift analysis (Doppler shift) provides feedback on the velocities, direction, and flow characteristics of the RBCs flowing through blood vessels encountered by the single dimension of the ultrasound beam. The continuous wave Doppler samples the flow of the entire ultrasonic beam path. The reflected signal frequency is altered by both the blood velocity and the difference signal, ie, the difference between the transmitting frequency and reflected frequency. In contrast to the continuous wave Doppler, there is the pulsed range-gated Doppler, designed so that a single transducer alternately sends and receives. Short bursts of ultrasound can be localized accurately and are depth controlled (Fig 8). The TCD is such a pulse range–gated Doppler.

The Doppler probe is coupled to the skin with an ultrasonic gel for efficient transmission and reception of the ultrasound signal (Fig 6B). If there is an insufficient amount of gel used, the signal being sent will be attenuated accordingly. Sound velocity in air is 343 m/s, whereas in soft tissue it is 1,540 m/s. For all practical purposes, air will prevent ultrasound transmission. Since air is an extremely poor conductor of the ultrasound wave, ample use of gel coupling between probe and skin is essential. More gel rather than too little is best. When insonating through hair, one should impregnate the gel thoroughly into the hair. This will help to eliminate air pockets between the probe and skin.

The TCD (Fig 6A) used in this study has the following major features:

1. Electronically adjustable depth control (depth gate) in 5-mm steps from 25 mm to 150 mm.
2. Acoustic intensity maximum of 100 mW/cm spatial peak, temporal average. This is adjustable between 10% and 100%.
3. The mean blood flow velocity can be read on the screen in centimeters per second or kilohertz.
4. Signal processed by a fast Fourier transformation with 64 points.
5. Choice of a unidirectional or bidirectional measuring scale.
6. Audio output from an external speaker or through a headphone.
7. Doppler direction control: blood flow toward or away from the Doppler probe.

The direction of RBC flow is displayed on the TCD screen by the symbols < = ⊏ and = > ⊏. The former signifies that the direction mode is set to designate RBC flow away from the probe, and the latter, RBC flow toward the probe.

In the probe construction, a concave polystyrene acoustic lens is applied to the barium titanate crystal and allows for a sonic focal point at a depth of 5.5 cm with a 3.5-mm lateral spread and a 5-mm axial spread. Recently, the EME Corporation electronically updated the TCD and probe to achieve stronger return signals, thus making trans-skull insonating easier to obtain and more accurate.

A 2-MHz probe offers a more effective reflection from the moving RBCs than a 1-MHz crystal. Even though a 1-MHz crystal has a more powerful bone penetration capability than a 2-MHz crystal, the reflected return signal is not as strong as with the 2-MHz crystal. It has been shown recently that a 1.5-MHz transducer does penetrate more effectively than the 2-MHz, albeit with a weaker return echo. However, if there is thick bone and too weak a return because of inadequate penetration with a 2-MHz transducer, a 1.5-MHz crystal may effectively send and receive the ultrasound information (R. Aaslid, personal communication, 1986).

Like anything else, the TCD requires a learning curve, and one becomes more adept as the patient experience increases. It is important to optimize the return signal so as to obtain the greatest intensity. By slowly moving the end of the probe from side to side, as well as up and down, or in a rotary manner, one can locate the thinnest bone (window). Large sweeping motions are to be condemned and easily can pass over the artery too rapidly.

Transcranial Doppler. The skull will attenuate the signal of a 5- to 10-MHz Doppler sufficiently to render it useless as a study of cerebrovascular blood flow velocity. The lower the Doppler resonance frequency, the greater the sonic energy and the less the attenuation through the bones of the skull. In 1981, Dr Rune Aaslid, the father of the TCD, was the first to use a 2-MHz Doppler probe on his own head and obtain, albeit a weak one, an arterial blood flow sonic echo. He used a cardiac Doppler. Fortuitously, his temporal bone was thin enough that he heard a weak vascular return signal on applying the probe to the skull in front of his ear. The article "Noninvasive Transcranial Doppler Ultrasound Recording of Flow Velocity in Basal Cerebral Arteries" was published by Aaslid et al[26] in 1982. By locating the thinnest area of bone, insonation will have less impedance by the bone and thus maximize transmission and signal return. The thinner areas of the temporal bone, the interosseous spaces between the skull base and atlas, and the orbit allow transmission of the ultrasound signal and have been termed windows. With this approach, the time mean blood flow velocity along the entire course of vessels such as the larger vertebrobasilar arteries, the circle of Willis, or the more peripheral middle cerebral

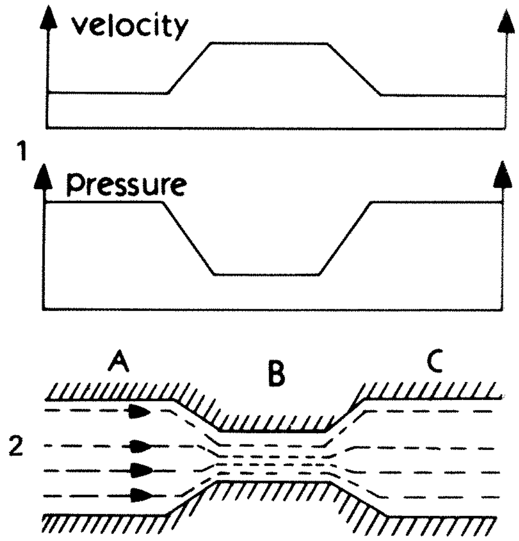


Fig 9. Physical correlates of flow velocity and pressure (1) with change in diameter within rigid tube (2). Decreased diameter seen in bottom diagram at point B is comparable to stenosis within artery.

artery (MCA) can be tracked sequentially in 5-mm segments. A sudden increase in time mean blood flow velocity signifies a narrowing of the lumen of the artery at that specific depth noted on the TCD. If the TCD designated the probe to measure flow "toward the probe" on following a vessel, this normally should display the return signal above the baseline. If the return signal is displayed below the baseline, this would imply that the blood is flowing away from the probe.

Basic Hemodynamics. Blood pressure and velocity of flow vary according to the size of the vessel lumen. A sudden narrowing of the lumen causes an increase in blood flow velocity while the blood pressure drops. Understanding this fundamental concept is basic in the use of the TCD for sequential tracking of the larger arteries of the brain (Figs 9 and 10[27]). Normally, blood flows in a laminar pattern in an artery. The laminar flow profile is parabolic in shape. There is maximum resistance to flow by the arterial wall at the periphery, with lesser friction of each more central layer, leaving the fastest flow at the central axis. However, where the vessel wall is not smooth and is roughened by atherosclerosis and/or a clot, the narrower lumen disrupts normal laminar flow and creates a poststenotic turbulent flow pattern with a diminution of flow velocity. The rapidly flowing approaching RBCs literally bump into the slower RBCs just distal to the roughened atherosclerotic lumen, broadly slowing the RBCs across most of the lumen. Here the parabolic (bullet) profile is changed to a flattened frontal (blunt) profile, because the entire uniform flow pattern has been abruptly and haphazardly slowed (Fig 11). The above series of events causes poststenotic vessel wall vibrations and can cause an audible bruit.

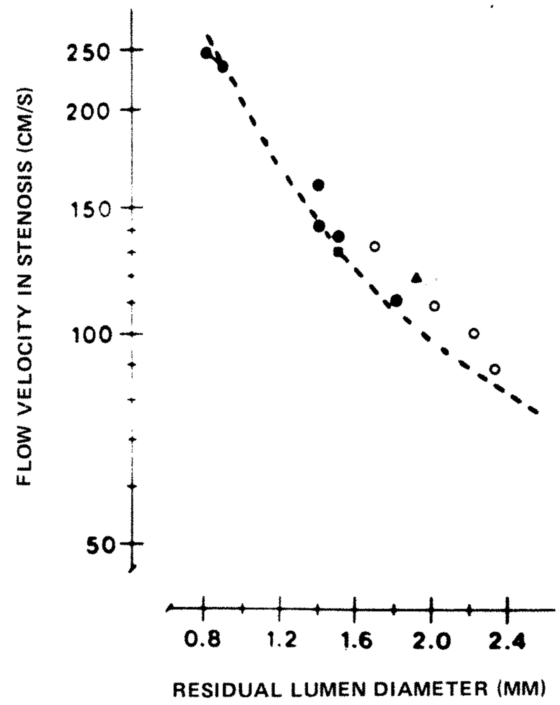


Fig 10. Relationship between transcranial Doppler velocity finding and residual lumen diameter of intracranial stenosis. Broken line represents regression line found in larger series on cerebral vasospasm. Filled circles — middle cerebral artery, filled square — anterior cerebral artery, filled triangle — basilar artery, open circles — carotid siphon. Logarithmic flow velocity scale. Flow velocity of 250 cm/s approximates 80% arterial stenosis, while flow velocity of 130 cm/s approximates 60% stenosis. Reproduced with permission.[27]

Video Display Flow Pattern Interpretations. In laminar flow, faster-flowing RBCs, in contrast to slower-flowing RBCs, can be detected by Doppler shift analysis. The TCD utilizes a spectral frequency analysis via fast Fourier transformation. The TCD has filtering capability for 64 different frequencies in fast Fourier transformation that display by point analysis on the screen. Thus, the velocity of the RBC reflected wave is displayed as the ordinate and is frequency related. The abscissa denotes time. The faster-flowing RBCs are displayed at the higher frequency of systole and diastole of the Doppler return echo of the arterial flow pattern, while the slower-moving RBCs are shown as lower frequencies. The RBC numbers or amplitude is displayed on the screen by the degree of whiteness, ie, in the sample insonated, no cells moving appear black at a given velocity, gray signifies a few cells

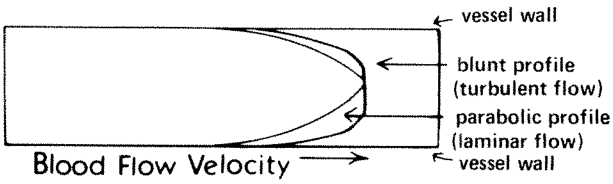

vessel wall
blunt profile (turbulent flow)
parabolic profile (laminar flow)
vessel wall
Blood Flow Velocity

Fig 11. Laminar, bullet (parabolic) profile versus turbulent, blunt profile.

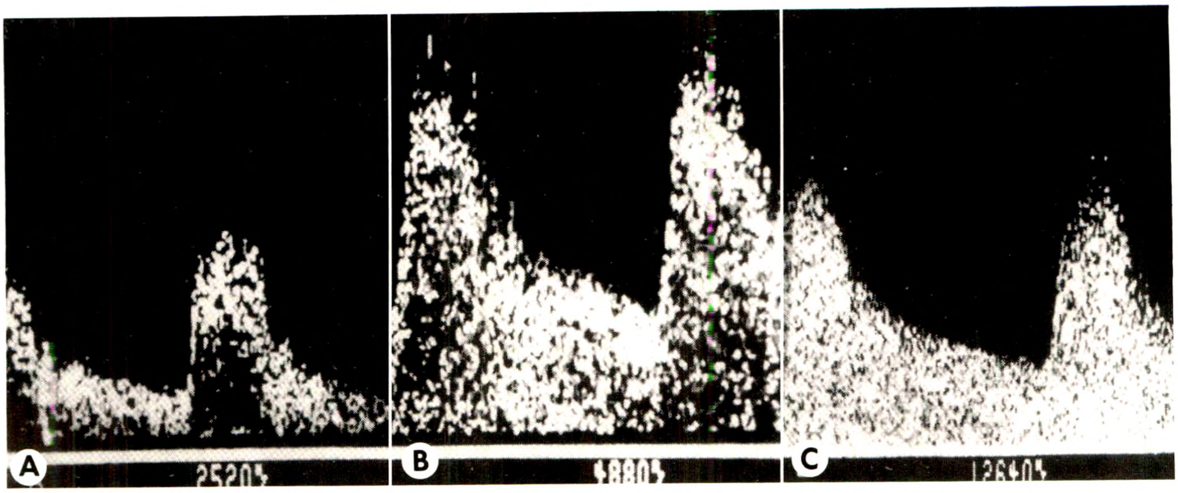


Fig 12. Phasic blood flow in common and internal carotid arteries as detected by continuous wave Doppler ultrasound spectral frequency analysis. Doppler frequency shift measurement is displayed on ordinate, time is on abscissa, and amplitude is represented by degree of "whiteness" of trace (ie, black represents no blood cells moving at given velocity, gray, few cells at that velocity, and white, many cells at that velocity). Peak velocity shift is 2,520 Hz in A, 4,880 Hz in B, and 12,640 Hz in C. Just under two cardiac cycles are shown. A) Blood flow in common carotid artery. During peak systole, most blood cells are moving within narrow velocity range, producing nearly blank area or "window" under systolic velocity profile. B) At internal carotid ostium flow velocity is normally slightly higher, and window, although still present, is less apparent because of slight turbulence produced by flow separation that occurs in carotid bulb. C) Blood flow in tight internal carotid stenosis. Peak Doppler shift is greater than 12 kHz, and uniform frequency distribution is present during systole, both consistent with high velocity turbulent flow distal to stenosis. Residual lumen diameter was 1.1 mm. Modified and reproduced with permission from Lees RS, Kestler JP. Noninvasive diagnosis of extracranial cerebrovascular disease. In: Barnett HZM, Stein B, Mohr J, Yatsu E, eds. *Stroke: Pathophysiology, Diagnosis and Management*. New York: Churchill Livingstone, 1986:257-68.

moving at that velocity, and white signifies most RBCs moving at this velocity. Thus, the greater the RBC velocity, the higher the spectral ordinate display of the waveform. The "whiter" the display, the greater the amplitude signifying that most of the RBCs are flowing at this specific velocity. Thus, high amplitude low frequency components of the spectral frequency analysis would display a greater white area at the inferior aspect of the ordinate axis at that specific time noted on the abscissa. Such a display would mean that most of the RBC velocity flow pattern has diminished (Fig 12).

It is important to realize that spectral frequency analysis is much more diagnostic of the hemodynamics with B-mode ultrasonographic imaging of the extracranial carotid arteries than studies with the TCD of the basal arteries of the brain. The small sample volume insonated via the B-mode yields reliable spectral frequency analysis, eg, systolic window or spectral distribution to assess low to moderate degrees of stenosis of the carotid bifurcation. However, it does not apply with comparable accuracy to the TCD display.[28]

It is important to re-emphasize that the time mean blood flow velocity in centimeters per second or in kilohertz on the TCD increases as the diameter of the lumen decreases. If a basal artery such as the VA is tracked sequentially up or down the brain stem in 5-mm steps and suddenly there is a marked increase in the time mean blood flow velocity, usually anything greater than either 80 cm/s or 2 kHz at a specific depth would signify a stenosis at this site. The higher the number, the greater the stenosis. An extremely severe stenosis secondary to vasospasm caused by subarachnoid hemorrhage may reach a time mean velocity as high as 350 cm/s. Following the vessel past the stenosis may now show a marked damping of the blood flow with diminished

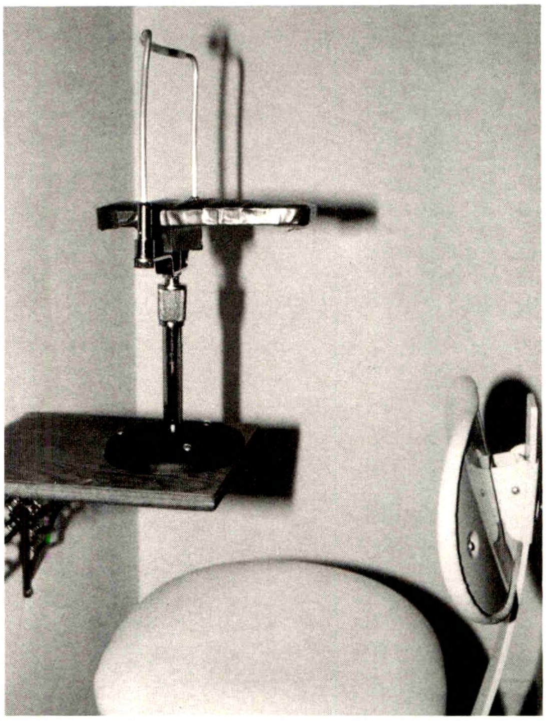


Fig 13. TCD head holder developed by author.

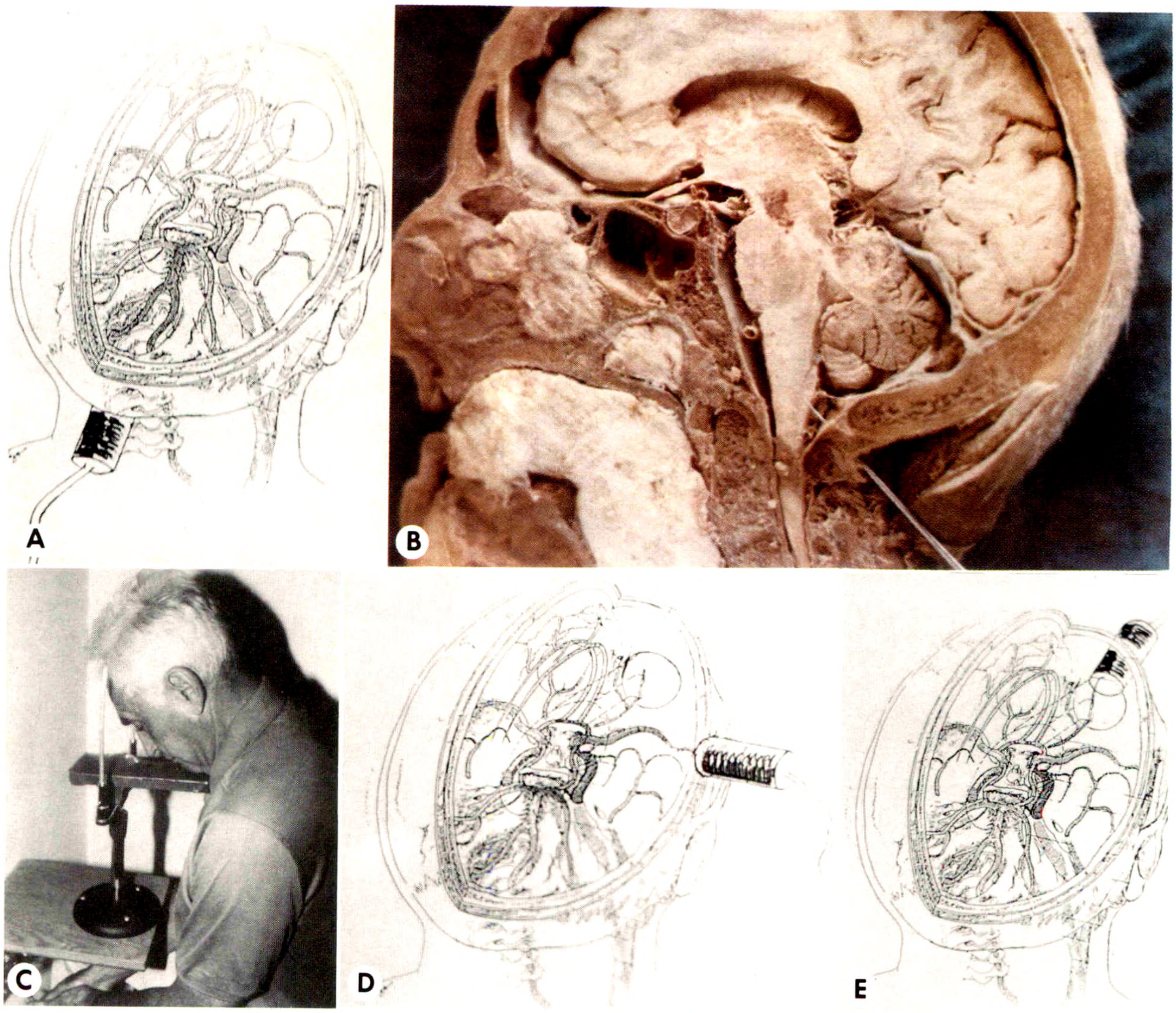


Fig 14. Windows. A) Foramen magnum window with probe at insonating site. B) Foramen magnum window with pick penetrating through window between atlas and midbase of occiput. C) Head secured in position for foramen magnum window with head holder. D) Temporal window with probe at insonating area. E) Orbital window.

pulsatility because of the poststenotic turbulence and the clamping effect of the stenotic lumen. If there was a complete stenosis, one might find a reverse flow pattern beyond the obstruction and hemodynamics of collateral circulation input.

Lindegaard et al[27] found the following flow velocities in normal cranial arteries in a population at risk: BA, 34 to 66 cm/s (median, 48 cm/s); MCA, 38 to 82 cm/s (median, 54 cm/s); anterior cerebral artery (ACA), 30 to 74 cm/s (median, 46 cm/s). They concluded that flow velocities from 35 to 80 cm/s represented the range for the normal intracranial arteries in a population at risk.

Blood flow velocity can be designated either in centimeters per second or by frequency (F) in kilohertz. The following formula for conversion is useful.

F x 39 = cm/s where F = frequency in kHz

Vessel Size. The BA and the intracranial ICA approximate 4 to 8 mm in diameter, while the MCA usually measures 3 to 4 mm. The AICA and the PICA approximate 2 mm, and the VA is 2 to 6 mm in diameter. The ophthalmic artery measures about 1 mm in diameter.

Length and lumen diameter of vessels are highly variable because of many factors, eg, anatomic variation, or size of the dominant vessel in contrast to the smaller or hypoplastic partner vessel. Also, the excess pressure head effect of hypertension can elongate the vessel. The BA has an average length of 33.1 mm and a lumen diameter of 4.1 mm. However, in patients with arteriosclerosis, the average lumen is 4.5 mm. In elderly people with arteriosclerosis and hypertension, the rostral end of the BA may extend upward toward the third ventricle and may indent it.[29]

Insonating With Head Support, Seated. One must optimize the sonic focal point to maximize the

TRANSCRANIAL DOPPLER INSONATING PARAMETERS

Window and Artery	*Usual Insonating Depth (mm)*	*Intensity (%)*
Foramen magnum and suboccipital*		
Vertebral (fourth part)	40-(65-75)	100
Basilar	(65-75)-(95-105)	
Posteroinferior cerebellar (variable; suspected takeoff)	50-55	
Anteroinferior cerebellar (suspected takeoff)	80	
Temporal		
Middle cerebral; anterior cerebral bifurcation	55-60	100
Middle cerebral trunk	45-50	
Trifurcation of middle cerebral	35-40	
Distal internal carotid siphon; anterior cerebral	60-65	
Posterior cerebral, ipsilateral	65	
Posterior cerebral, contralateral	75-80	
Posterior communicating	60-70	
Anterior communicating	70-75	
Superior cerebellar	65-70	
Orbital		
Ophthalmic	40-45	25
Genu of internal carotid siphon	65	
Extracranial vertebral		
Second part (distal, axis to atlas)	30-40	100
Third part (suboccipital triangle)	30-40	100

Above measurements for foramen magnum window may vary: nuchal musculature development and subcutaneous fat vary from patient to patient, besides sex differences. Thus, insonating depth measurements will vary accordingly.

*Suboccipital window approximates foramen magnum window within skull.

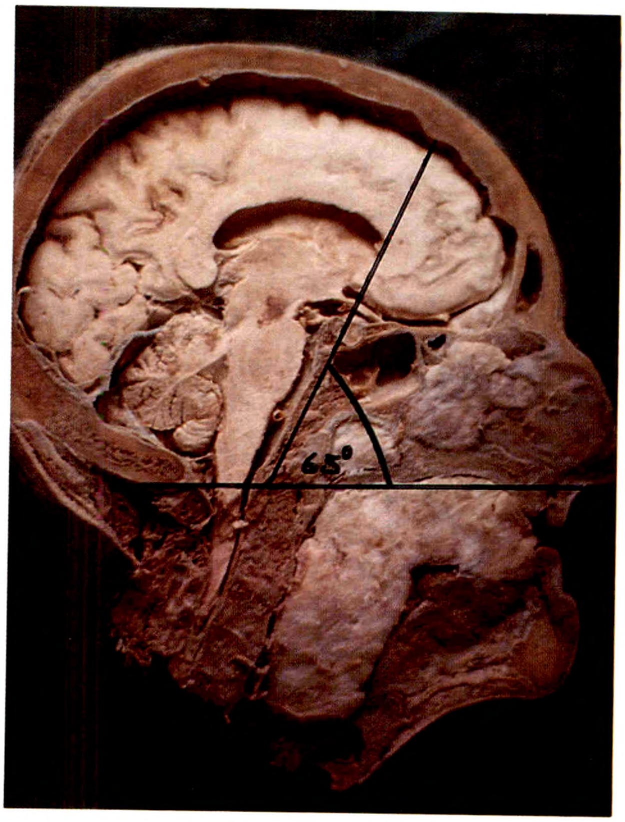


Fig 15. Clivus makes 65° anterior angle with naso-occipital line. External auditory meatus points to approximate midpoint of clivus.

reflected echo, so again scanning with small movements of the probe will be most rewarding. Also, it is best to keep the head as steady as possible in order to find the most favorable sonic site. Once it is located, should the head move, the optimal signal can be lost. The author has devised a table with a chin-forehead support similar to that used by the ophthalmologist. The chin support was elongated. The base of this device is incorporated securely with the top of the table so as to immobilize the unit. With this device, the head is fixed when the probe is applied to the various windows for study (Fig 13).

Windows. There are three standard TCD approaches (windows) that are used routinely to insonate the larger basal arteries of the brain: 1) the foramen magnum window (Fig 14A-C); 2) the temporal window (Fig 14D); and 3) the orbital window (Fig 14E). The suboccipital window enhances a study of the foramen magnum window especially for the third and fourth segments of the VA (see Table).

Technique for Insonating Foramen Magnum Window. The foramen magnum window allows ultrasound to pass through the foramen magnum. The probe is seated so as to insonate the area between the occiput and the atlas (at the midbase of the skull). At times, better signals may be received by placing the probe just off center, to either the right or left. Six finger-breadths below the inion, or a line drawn to the midline one finger-breadth below the tip of the mastoid process, is the usual foramen magnum window site. By sliding the index finger inferiorly off the midline of the base of the occiput, the bony, more superficial prominence first felt and most sensitive to the patient is the spinous process of the axis, and not the atlas; superoanteriorly lies the recessed atlas. With the neck in hyperflexion and the chin as close to the chest as possible, the atlas-occipital space will be more patent, thus presenting less bony impedance to the Doppler signal.

Since the VA and BA approximate the course of the clivus, some external landmarks are helpful. A line is drawn from the inferior aspect of the squamous occipital cortex to the base of the nose (the naso-occipital line). The clivus is measured along its posterior surface. The clivus subtends at an approximately 65° anterior angle to the naso-occipital line. This anterior angle may be as acute as 40° in the norm. It slopes upward from the foramen magnum (a portion of the basilar part of the occipital bone [os occipitale]) to the dorsum sellae (body of sphenoid bone). Inferiorly, the clivus begins approximately 40 mm from the skin superior to the upper surface of the atlas (Fig 15). The external auditory meatus points to the approximate midpoint of the clivus, and the pontomedullary junc-

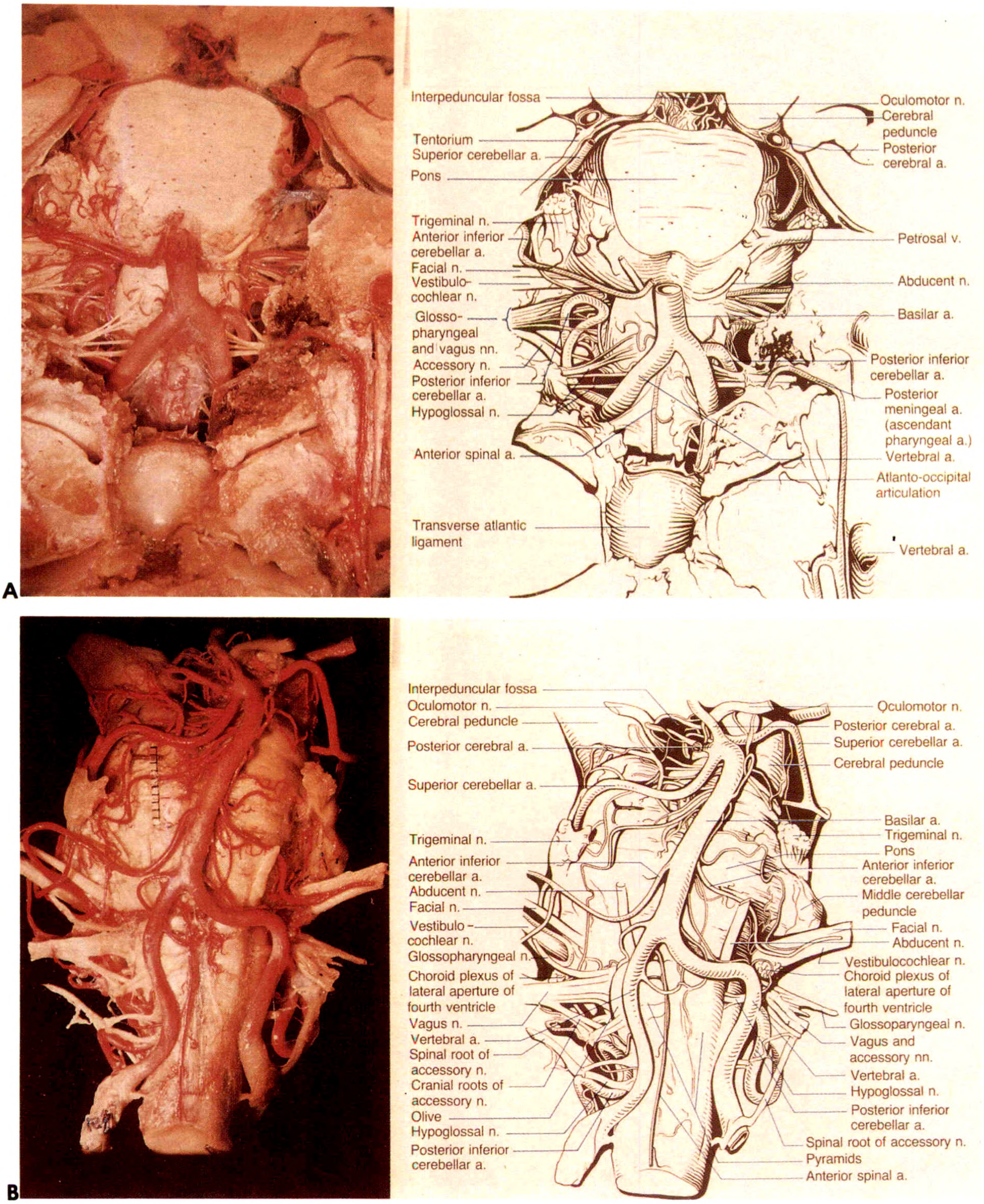


Fig 16. Posterior inferior cerebellar artery (PICA). Reproduced with permission from Koos WT, Spetzler RF, Pendl G, Perneczky A, Lang J. *Color Atlas of Microneurosurgery*. New York: Thieme, 1985:295. A) Craniocervical junction, basal view. PICA takeoff can vary among patients, as well as between right and left vertebral arteries in same patient. B) PICA takeoff variation and vessel size differences. Note larger-diameter PICA on right side of picture and smaller anterior inferior cerebellar artery on same side in contrast to opposite vasculature.

tion is found at this site. With the chin on the chest, the probe should be directed to the foramen magnum window as follows. The probe should be seated in the suboccipital sulcus just above the spinous process of the atlas, then directed in line with the external auditory meatus and/or 5 cm above the nasion. This will follow the general plane of the clivus. The following arteries are insonated: the fourth part of

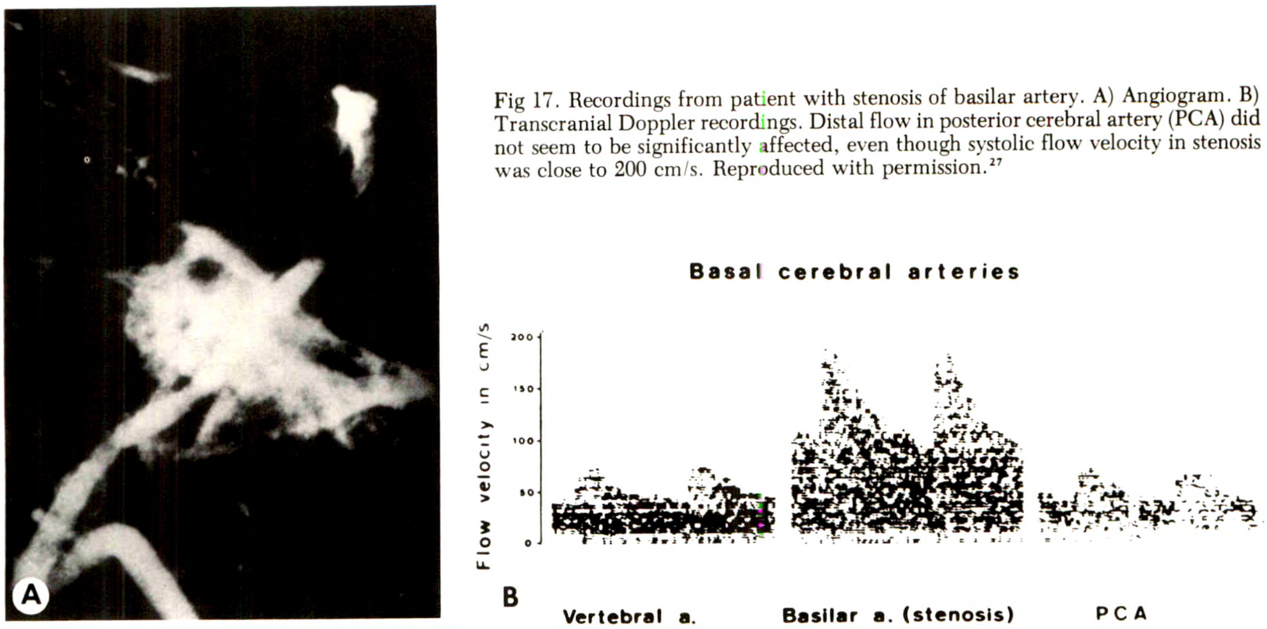


Fig 17. Recordings from patient with stenosis of basilar artery. A) Angiogram. B) Transcranial Doppler recordings. Distal flow in posterior cerebral artery (PCA) did not seem to be significantly affected, even though systolic flow velocity in stenosis was close to 200 cm/s. Reproduced with permission.[27]

the VA (intracranial), the BA, and the anatomic sites of the PICA and the AICA. The foramen magnum window and the suboccipital window are the most important windows to interrogate for the large basal arterial circulation to the brain stem and cerebellum. If no return signal is received, the head should be placed in the normal position or even in extension, and a "soft spot" may be found with ample return signal. This has been found with the elderly and may open up a hypertrophic osteoarthritic block or allow transmission through the thin bone of the external occipital squama. This technique also removes the prominence of the tensed nuchal ligament and permits a more stable seating of the probe.

The fourth part of the VA usually is insonated at depths of 40 mm; then the vessel is ascended to 65 to 75 mm, where the two VAs join to form the BA. The probe is tilted a few millimeters to the right or left in tracking the right or left VA, respectively. Seventy-five millimeters is usually the depth of origin of the BA; however, this is variable. A descending approach to locate the VA can be used, by finding the BA at 80 to 90 mm and insonating via a retrograde course to the VA. The PICA (at its usual anatomic locale) may be displayed below the baseline at a depth of 50 to 55 mm (reverse flow) when Doppler shifts from the VA are measured "away from the probe." The PICA takeoff can vary from patient to patient, as well as branch topographically at different sites from the right and left VA in the same patient (Fig 16). The AICA usually originates from the BA at 80 mm, but may arise from the distal VA at 65- to 70-mm depths. The BA may be tracked rostrally up to 100 mm. Time mean flow velocity is usually 34 to 66 cm/s for the normal BA.

The terminal part of the second part (cervical) of the VA as it traverses from the transverse foramen of the axis to the transverse foramen of the atlas can be insonated approximately one finger's breadth or 10 mm anterior and two fingers' breadth inferior to the tip of the mastoid process at a depth of 25 to 35 mm.

Suboccipital Window. The transverse process of C-1 is 10 mm anterior and slightly inferior and deep to the tip of the mastoid process. The styloid process is just anterior and deep to the transverse process of C-1. The third part of the extracranial VA (the part most vulnerable to neck rotation) as it exits from the transverse foramen of the atlas onto its posterior arch is found approximately 10 mm below the tip of the mastoid process and is insonated at a depth of 25 to 35 mm. If flow direction mode is set "away from the probe," signals may be found above and below the line, because the vessel is so tortuous at this site that one observes flow both toward and away from the probe. Now the probe should be placed posteromedial to the above site, just inferior to the insertion of the sternocleidomastoid muscle onto the posterior surface of the mastoid process. There is a soft depressed area, approximately 10 mm below the tip of the mastoid and three index fingers' depth (30 mm) posteromedial. The patient forcefully rotates his or her head (opposite to the side being insonated) against a hand held firmly on the patient's chin preventing rotation. Now the sternocleidomastoid muscle insertion area, on the side counter to the head rotation, will stand out in bold relief, and the insonating pocket site will be located at this suboccipital window site. This will allow insonation of the third part of the VA, where the vessel sits on the VA sulcus on the superior aspect of the posterior

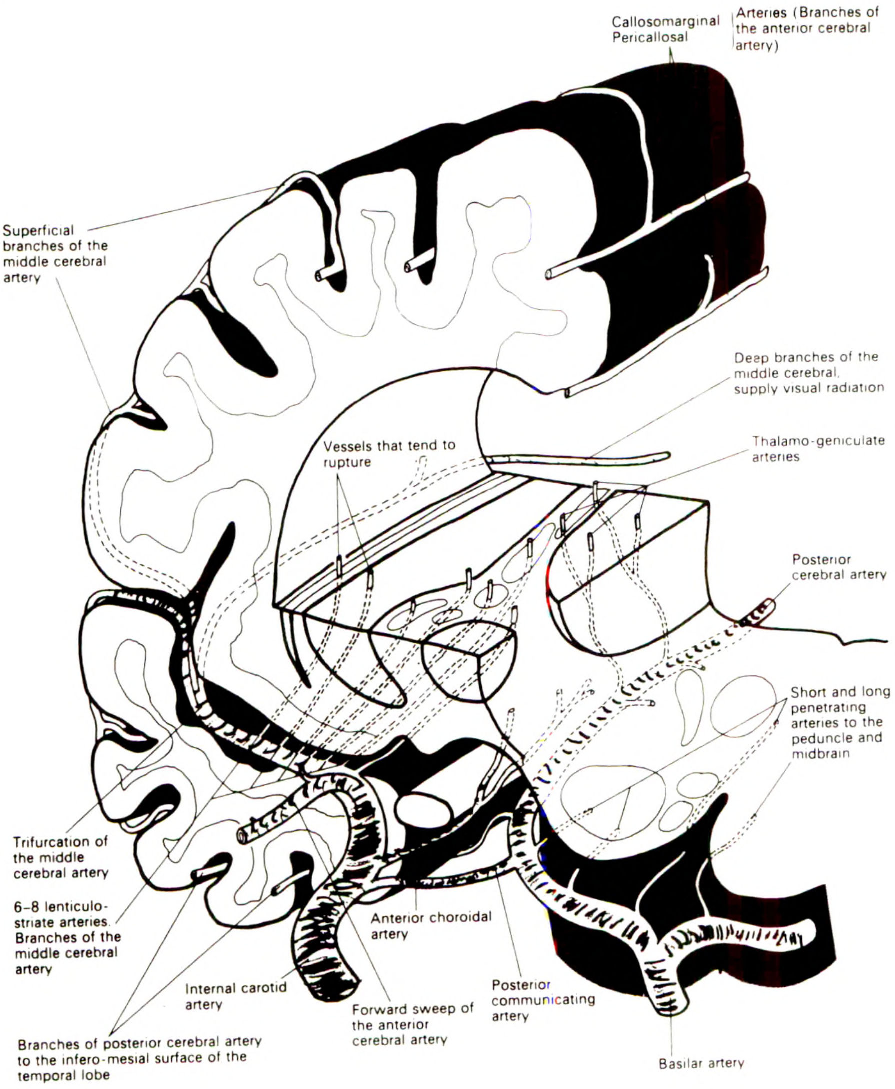

Callosomarginal
Pericallosal
Arteries (Branches of the anterior cerebral artery)
Superficial branches of the middle cerebral artery
Deep branches of the middle cerebral, supply visual radiation
Thalamo-geniculate arteries
Vessels that tend to rupture
Posterior cerebral artery
Short and long penetrating arteries to the peduncle and midbrain
Trifurcation of the middle cerebral artery
6–8 lenticulo-striate arteries. Branches of the middle cerebral artery
Anterior choroidal artery
Internal carotid artery
Posterior communicating artery
Forward sweep of the anterior cerebral artery
Branches of posterior cerebral artery to the infero-mesial surface of the temporal lobe
Basilar artery

Fig 18. Blood supply of deep structures of hemisphere. Reproduced with permission from Patten J. *Neurological Differential Diagnosis*. New York: Springer-Verlag, 1977:89.

arch of the atlas in the suboccipital triangle and then ascends superomedially into the foramen magnum. With the probe locked in at this site or at the terminal part of the second part of the VA, the head can be rotated to the extreme right or left, or be hyperextended to permit observation of any damping of the waveform with slow flow characteristics caused by proximal pathologic VA compression. This is difficult to perform because of the probe's shifting with the head movement. However, if it is carried out slowly the returned signal can be maintained. Also, the head initially can be placed in the desired final test position and now the probe can be seated with the head maintained in the desired position. The depth gate desired on the TCD is usually 35 mm. The probe is maintained at this suboccipital window site and directed toward the opposite orbit. It is suggested that this suboccipital site be termed the right or left suboccipital window, so as not to confuse it with the foramen magnum window (see Table). One can track the VA as it ascends into the cranium through the foramen magnum and look for any pathologic flow characteristics, eg, reverse flow or increased flow velocity. The opposite VA should be insonated similarly. Once a vessel has been located with the optimized echo, one should lock in the probe and track the vessel by changing the depth control on the TCD. Minimal subtle variations of the probe maintain the most intense signal during tracking. Figure 17 shows an angiogram of a stenotic BA with the TCD recordings.

Temporal Windows. These are found just above the zygomatic arch and usually never higher than 2.5 cm. There are three windows: anterior, middle, and posterior. The search is for the thinnest bone area. The blood flow direction mode setting is "toward the probe." The posterior window falls into the depression above the zygomatic arch just anterior to the auricle. The anterior window is posterior to the frontal process of the zygomatic bone. The middle window is between the two. The posterior window is usually best to use for elderly patients and lies slightly superior to the other two windows, and the probe is directed anteriorly. The probe is directed minimally posteriorly for the ante-

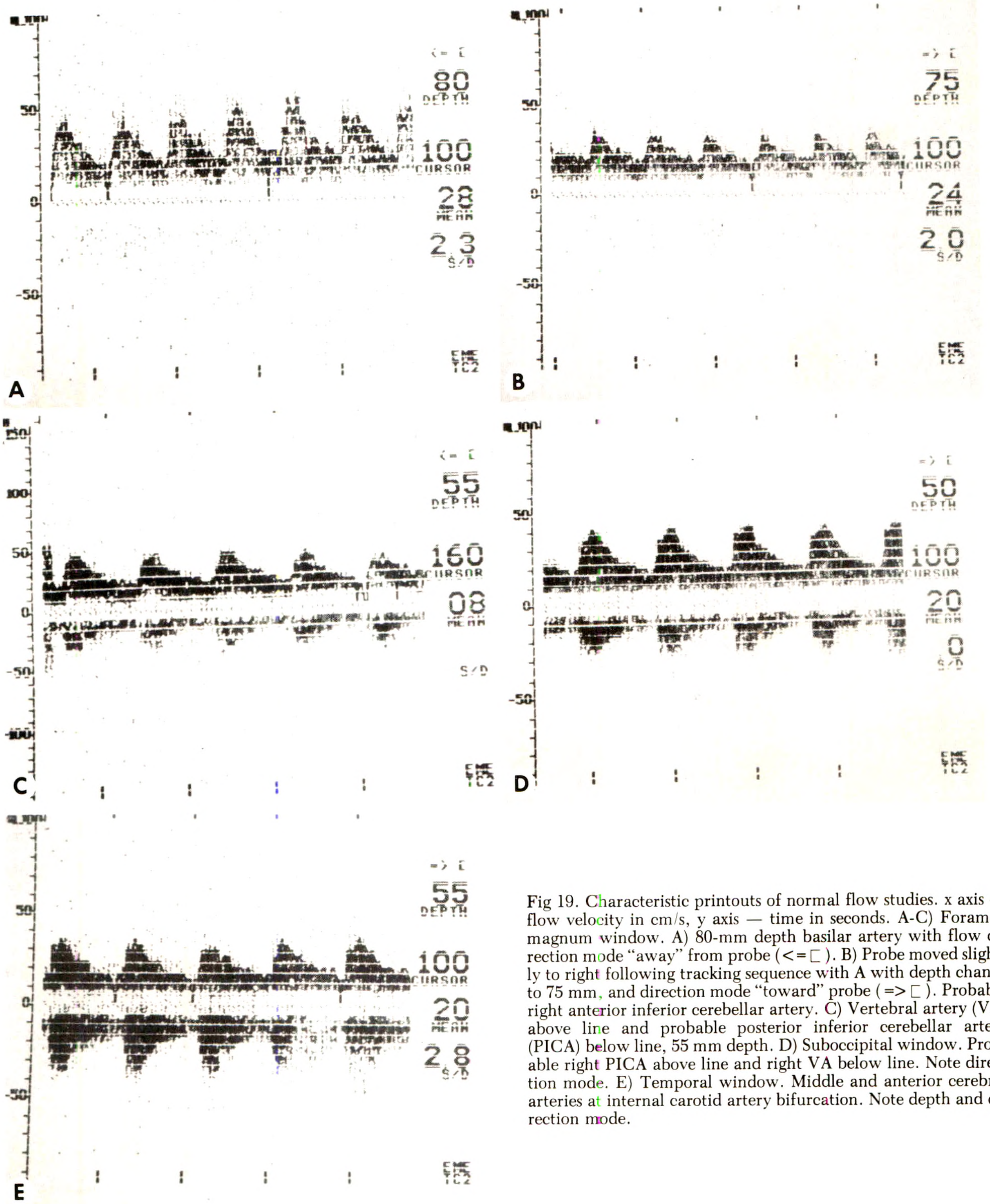


Fig 19. Characteristic printouts of normal flow studies. x axis — flow velocity in cm/s, y axis — time in seconds. A-C) Foramen magnum window. A) 80-mm depth basilar artery with flow direction mode "away" from probe (<=[ ). B) Probe moved slightly to right following tracking sequence with A with depth change to 75 mm, and direction mode "toward" probe (=>[ ). Probable right anterior inferior cerebellar artery. C) Vertebral artery (VA) above line and probable posterior inferior cerebellar artery (PICA) below line, 55 mm depth. D) Suboccipital window. Probable right PICA above line and right VA below line. Note direction mode. E) Temporal window. Middle and anterior cerebral arteries at internal carotid artery bifurcation. Note depth and direction mode.

rior window, while the probe is pointed directly medial for the middle temporal window.

The MCA has the highest blood volume flow to the cerebral hemisphere from the circle of Willis, transporting about 80%. It branches toward the probe, coming from the bifurcation of the terminal ICA into the MCA and ACA. The latter branches opposite the MCA (Fig 18). The ACA continues anteriorly before it ascends. This bifurcation of the ICA into the MCA and the ACA usually is insonated at a depth of 55 to 60 mm. The distal ICA siphon (supraclinoid segment) and ipsilateral posterior cerebral artery (PCA) can be found at a depth of 65 mm. The MCA waveform will display above the line, and the ACA will display below the line because with the latter the RBCs are flowing in an opposite direction. The MCA branches laterally and slightly anterior through the sylvian fissure and is tracked to lesser Doppler depths. The peripheral MCA trifurcation is insonated at a depth of 35 to 40 mm. A 45- to 50-mm depth is the main trunk of the MCA, with a time mean velocity of 54 cm/s in the normal artery. Usually as one insonates medially past and slightly inferior to the MCA-ACA bifurcation, ie, a 60- to 65-mm depth, the distal ICA siphon is located 10 to 20 mm below the bifurcation. The RBC flow direction plus spectral pattern always should be noted. The ipsilateral PCA is approximately 5 mm deeper than the ICA bifurcation, usually at a 65-mm depth, and the probe is directed slightly posterior and inferior. In the proximal segment of the PCA, blood normally will flow toward the probe, and as the vessel curves posteriorly, flow will be away from the probe. The contralateral PCA is found by tilting the probe medially at a 75-to 80-mm depth. One-half centimeter below the ipsilateral PCA, the ipsilateral SCA may be insonated at a 65- to 70-mm depth, and its contralateral vessel, 10 to 15 mm medially. Flow velocity in the PCA is altered 10% to 20% when the patient opens and closes his or her eyes. The PCA supplies the visual pathways. That this is not the case with the SCA is an aid in distinguishing it from the PCA.

The ACA at the bifurcation normally displays RBC flow away from the probe. If the flow is toward the probe as one keeps tracking the ACA anteriorly, it denotes an ipsilateral ICA severe stenosis or occlusion. The opposite ACA will have a significant increase in flow velocity as a hemodynamic response for collateral supply. Under normal conditions, compression of the ipsilateral common carotid artery in the neck reverses the flow pattern when the ACA is insonated (on the compressed artery side) and denotes a physiologically hemodynamic-functioning anterior communicating artery. The ACA can be tracked anteriad 70 to 80 mm. Usually after 80 mm there is a crossover past the midline, and the opposite ACA is received. The anterior and posterior communicating arteries may also be detected at depths of 70 to 75 mm and 60 to 70 mm, respectively. The success rate on insonating the temporal window is around 80% in the United States. However, in Switzerland and Germany a success rate of 95% is being achieved (R. Aaslid, personal communication, 1986), probably because of a longer experience time. The author finds this temporal window the most difficult of all the windows to insonate consistently and effectively. As the equipment improves, so will the success rate of insonating the temporal window. If electroacoustically possible, insonating in 1-mm steps rather than 5-mm steps would be more informative, as well as initiating the return echo at a 10-mm depth instead of the present 25-mm depth.

Orbital Window. The ultrasound intensity is lowered to 25% for this study, as a lens safety precaution. Contact lenses should be removed prior to the examination. The probe is placed over the closed eyelid with ample gel, so not to exert excessive pressure on the eyeball or squeeze out the gel and lose coupling efficiency. The base of the probe should be seated gently on the midinferior bony rim of the orbit onto the closed eyelid, and the probe is directed superomedially toward the optic canal. The nontest eye should be kept open and fixed at a distant object so as to immobilize both eyes. This seating helps to stabilize the probe. A 40- to 45-mm depth insonates the ophthalmic artery with a waveform typical of an extracranial vessel, ie, diastole close to the baseline because of the increased peripheral resistance and increased spectral density for the low frequencies because of flow deceleration. Flow normally should be toward the probe, but reversed with a critical ipsilateral ICA stenosis. Tracking the ophthalmic artery deeper, one can locate the genu of the siphon at a 65-mm depth and anatomically follow it. The parasellar ICA (proximal siphon) is traced as the probe signals proceed inferiorly.[30]

Figure 19 shows some characteristic printouts of normal flow studies for the above windows.

The neurotologist should listen almost routinely with a stethoscope for the presence of a bruit both at the internal carotid bulb area and at the medial third of the supraclavicular area, which is the site of origin of the first part of the SCA, from which the VA most usually arises. One must remember that it is possible for a bruit that is transmitted from the cardiac aorta area to mask out a coexisting SCA or ICA bulb bruit. Also, palpate for the consistency of the right and left common arteries and ICAs. Especially note whether the vessel is soft and pliant or rigid and/or sclerotic, and at which sites. Also compare the pulse amplitude below the carotid bulb as well as above it. Likewise, compare the relative difference between the right and left sides. If possible try to detect the phasic linear expansion of the artery, which normally widens the vessel in a horizontal manner. If the vessel lumen is critically stenotic or occluded at the carotid bulb, the obstruction to blood flow now causes an abrupt backflow, which creates a vertical pulsation in the common carotid artery. Here a markedly diminished or absent pulse will be detected above the obstruction in the ICA. Auscultation is indicated especially in the high risk older patient. Optimally, the neurotologist should be capable of following through with B-mode ultrasound investigation of the extracranial carotids with spectral frequency analysis of blood flow. Proficient use of the TCD, especially for evaluation of the status of the vertebrobasilar artery circulation, can be helpful in separating vascular disorders from other causes that affect the vestibular system. Finally, the bonus of assisting in the prevention of a catastrophic stroke will be extremely rewarding to both patient and neurotologist.

Transcranial Doppler ultrasonography appears to be a technique that is growing rapidly. Most of the pioneering work was directed to the anterior circulation. The importance of gleaning information about the vertebrobasilar circulation is obvious for the neurotologist. As the technology and instrumentation advance, the information gained for investigating the posterior circulation also will improve. The TCD has become a welcome additional noninvasive tool.

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APPENDIX

ADOLF WALLENBERG, 1862-1949
(Reproduced with permission.[1])

Adolf Wallenberg was the oldest of four sons whose father was a physician. He was born on Nov 10, 1862, in Danzig, Germany. At his death he had published 67 articles, 63 written by himself and four he coauthored. His most famous article was published in 1895, when he was 33 years old. The paper, "Acute Bulbar Disturbance (Embolus of the Left Posterior Inferior Cerebellar Artery?)," presented one case history of a 38-year-old man and outlined all the various symptoms and relative pathways involved. Wallenberg postulated that the patient's infarct was caused by an occlusion of the posterior inferior cerebellar artery, perhaps by an embolus, where it branches from the vertebral artery. Wallenberg studied seven injected brains in order to outline the course of the posterior inferior cerebellar artery. He also reviewed the literature presenting similar clinical findings and medullary lesions. It is notable that he was astute enough to place a question mark after posterior inferior cerebellar artery in his title, although whether he was questioning the existence of an embolus or the identity of the artery involved, is not certain. Wallenberg verified the suspected arterial occlusion and medullary infarction and published the necropsy findings in 1901. Since that time, the entity has been termed the Wallenberg syndrome.

This apparently quiet man of diminutive stature maintained his own laboratory in a small room in his home. Later, he transferred his research to the Danzig General Hospital, of which he became the Director in 1907. He first opened an office and practiced general medicine in Danzig in 1885. He ultimately became a self-made neurologist. In 1929, Dr Wallenberg received the highest award given by the German Neurological Society, the Wilhelm Erb Medal. Yet he had no university affiliation. He had to resign from the hospital upon reaching age 65.

All of his research ceased in 1934, when he was forbidden by the Nazis to work or to publish. Fortunately, he left Germany a few days before the outbreak of the war in 1939, went to Oxford, England, and then arrived in the United States in 1943. Here, he and his wife resided in Manteno, Illinois, where he joined his daughter, Dr Marianne Wallenberg, Clinical Director of Manteno State Hospital.

He was made an honorary member of The Chicago Neurological Society in 1944 and subsequently signed a contract donating his entire library and slide collection to the University of Illinois College of Medicine. Unfortunately, it was learned via the Polish Embassy in Washington, DC, that the storehouse in Danzig containing all of Wallenberg's materials had been bombed and destroyed totally.

Dr Wallenberg developed angina pectoris and died April 10, 1949, not quite 87 years of age. He was an industrious, honest investigator, who died as he lived, inconspicuously. At his funeral services the speaker eulogized this world famous physician quite aptly in his culminating three words, "a noble gentleman."[1]

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COMPARISON OF SENSORY AIDS IN DEAF CHILDREN

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TELEPHONE SPEECH COMPREHENSION WITH USE OF THE NUCLEUS COCHLEAR IMPLANT

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AUDIOLOGIC RESULTS FOLLOWING REIMPLANTATION OF COCHLEAR IMPLANTS

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ANNALS
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COMPARISON OF SENSORY AIDS IN DEAF CHILDREN

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A speech perception hierarchy has been developed and applied to assess the influence of cochlear implants and tactile aids on the acquisition of auditory, speech, and language skills in deaf children. Encouraging improvements were noted with both types of sensory aids at the detection level. The House 3M and Nucleus cochlear implant designs appear to offer advantages over the Tactaid II in providing ancillary speech perception cues to deaf children. Preliminary observations suggest that the multichannel cochlear implant design may be superior to the single-channel coding scheme.

KEY WORDS — cochlear implant, hearing, language, sensory aid, speech.

The influence of various sensory aids on the acquisition of auditory, speech, and language skills in deaf children has been the focus of a comprehensive longitudinal study. Because of the heterogeneity of the study population and the fact that these skills typically develop slowly and imperfectly in deaf children, a hierarchic progression of test measures has been developed and applied.

Performance with a wearable two-channel vibrotactile device, the Tactaid II, which converts sound to vibrations sensed by the skin, is compared to performance with two cochlear implant designs, the House 3M and Nucleus 22-channel devices, which convert sound to electrical signals transmitted to the cochlear nerve through an implantable intracochlear electrode array.

TABLE 1. SUBJECT CHARACTERISTICS

Subject	*Length of Use of Aid (yr)*	*Age at Onset of Deafness (yr)*	*Length of Deprivation (yr)*	*Age at Fitting of Aid*
Subjects with Tactaid II device				
1	3.5	4.0	1.5	5.5
2	3.0	1.0	9.2	10.2
3	2.0	0.0	10.6	10.6
4	1.5	0.5	3.6	4.1
5	1.5	3.0	3.3	6.3
6	1.0	0.0	8.0	8.0
7	1.0	0.0	4.1	4.1
8	1.0	0.0	6.1	6.1
9	1.0	0.0	11.6	11.6
10	1.0	2.5	3.6	6.1
11	1.0	2.2	3.8	6.0
12	1.0	1.9	2.1	4.0
13	1.0	3.3	0.3	3.6
14	0.5	0.0	6.1	6.1
Subjects with House 3M cochlear implant				
15	5.0	6.0	5.5	11.5
16	4.5	0.0	4.5	4.5
17	4.5	5.7	1.6	7.3
18	4.0	0.8	10.7	11.5
19	4.0	1.5	9.3	10.8
20	4.0	1.6	7.1	8.7
21	3.0	0.0	3.0	3.0
Subjects with House 3M cochlear implant (cont'd)				
22	3.0	0.0	12.5	12.5
23	2.5	0.0	2.5	2.5
24	2.5	2.3	10.6	12.9
25	2.0	0.5	2.8	3.3
26	2.0	1.3	2.6	3.9
27	2.0	1.3	3.2	4.5
28	2.0	5.3	1.0	6.3
29	2.0	2.8	2.5	5.3
30	1.5	2.0	4.0	6.0
31	1.0	6.7	1.3	8.0
32	0.5	1.3	8.8	10.1
Subjects with Nucleus 22-channel cochlear implant				
33	3.5	1.5	2.6	4.1
34	1.5	0.0	11.1	11.1
35	1.0	0.0	4.9	4.9
36	1.0	0.3	6.9	7.2
37	1.0	1.8	2.5	4.3
38	1.0	2.8	3.5	6.3
39	0.5	0.5	4.9	5.4
40	0.5	1.3	5.8	7.1
41	0.5	2.8	10.4	13.2
42	0.5	0.0	6.7	6.7

From the Department of Otolaryngology–Head and Neck Surgery, Indiana University School of Medicine, Indianapolis. Supported by grants from the James Whitcomb Riley Memorial Association, Indiana Lions, Psi Iota Xi, Indiana University Foundation–DeVault Otologic Research Fund, and National Institutes of Health grant NS 24875.

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TABLE 2. AIDED WARBLE TONE THRESHOLDS (dB SPL)

		Frequency (Hz)					
Subject	*Ear*	*250*	*500*	*1,000*	*2,000*	*3,000*	*4,000*
Subjects with Tactaid II device							
1	R	91	97	NR	NR	NR	NR
	L	91	97	NR	NR	NR	NR
2	R	91	102	NR	NR	NR	NR
	L	91	102	NR	NR	NR	NR
3	R	78	62	57	101	NR	NR
	L	72	107	NR	NR	NR	NR
4	R	NR	NR	NR	NR	NR	NR
	L	NR	NR	NR	NR	NR	NR
5	R	83	NR	NR	NR	NR	NR
	L	83	NR	NR	NR	NR	NR
6	R	88	84	NR	NR	NR	NR
	L	88	84	NR	NR	NR	NR
7	R	83	96	NR	NR	NR	NR
	L	83	96	NR	NR	NR	NR
8	R	56	69	NR	NR	NR	NR
	L	73	89	NR	NR	NR	NR
9	R	58	59	55	102	120	124
	L	66	64	55	NR	NR	NR
10	R	NR	NR	NR	NR	NR	NR
	L	NR	NR	NR	NR	NR	NR
11	R	70	80	NR	NR	NR	NR
	L	70	80	NR	NR	NR	NR
12	R	72	76	90	NR	NR	NR
	L	74	96	95	NR	NR	NR
13	R	NR	NR	NR	NR	NR	NR
	L	NR	NR	NR	NR	NR	NR
14	R	50	70	80	NR	NR	NR
	L	50	70	80	NR	NR	NR
Subjects with House 3M cochlear implant							
15	(R)	75	88	NR	NR	NR	NR
	L	84	NR	NR	NR	NR	NR
16	(R)	84	104	NR	96	NR	NR
	L	84	104	NR	96	NR	NR
17	(R)	NR	NR	NR	NR	NR	NR
	L	NR	NR	NR	NR	NR	NR
18	(R)	NR	NR	NR	NR	NR	NR
	L	72	72	77	104	NR	NR
19	(L)	66	86	84	101	NR	NR
	R	76	95	96	NR	NR	NR
20	(L)	75	79	NR	NR	NR	NR
	R	91	104	NR	NR	NR	NR
21	(L)	79	79	NR	NR	NR	NR
	R	79	85	NR	NR	NR	NR
Subjects with House 3M cochlear implant (cont'd)							
22	(L)	NR	102	94	NR	NR	NR
	R	74	104	86	NR	NR	NR
23	(R)	87	98	NR	NR	NR	NR
	L	78	84	NR	NR	NR	NR
24	(L)	84	NR	NR	NR	NR	NR
	R	86	92	NR	NR	NR	NR
25	(R)	90	101	NR	NR	NR	NR
	L	85	89	100	NR	NR	NR
26	(R)	NR	NR	NR	NR	NR	NR
	L	82	82	NR	NR	NR	NR
27	(R)	78	95	NR	NR	NR	NR
	L	73	94	NR	NR	NR	NR
28	(R)	86	95	NR	NR	NR	NR
	L	82	92	NR	NR	NR	NR
29	(L)	NR	NR	NR	NR	NR	NR
	R	NR	NR	NR	NR	NR	NR
30	(L)	90	100	NR	NR	NR	NR
	R	85	100	NR	NR	NR	NR
31	(R)	82	98	NR	NR	NR	NR
	L	87	105	NR	NR	NR	NR
32	(R)	89	74	68	84	NR	NR
	L	77	96	NR	NR	NR	NR
Subjects with Nucleus 22-channel cochlear implant							
33	(R)	82	87	NR	NR	NR	NR
	L	81	92	NR	NR	NR	NR
34	(R)	88	87	NR	NR	NR	NR
	L	87	89	NR	NR	NR	NR
35	(L)	84	NR	NR	NR	NR	NR
	R	87	NR	NR	NR	NR	NR
36	(L)	86	96	NR	NR	NR	NR
	R	81	NR	NR	NR	NR	NR
37	(L)	80	95	NR	NR	NR	NR
	R	82	93	NR	NR	NR	NR
38	(L)	73	69	NR	NR	NR	NR
	R	76	74	NR	NR	NR	NR
39	(R)	NR	NR	NR	NR	NR	NR
	L	NR	NR	NR	NR	NR	NR
40	(R)	64	72	73	87	74	80
	L	63	66	64	72	NR	NR
41	(R)	NR	NR	NR	NR	NR	NR
	L	NR	NR	NR	NR	NR	NR
42	(L)	95	93	84	79	87	NR
	R	80	83	79	89	87	NR

Parentheses indicate ear later receiving implant.

NR — no response at audiometric limits.

PATIENTS AND METHODS

PATIENTS

All subjects were profoundly deaf children who received no benefit from conventional hearing aids. Typically, the children demonstrated either no response or responses at levels suggestive of vibrotactile rather than auditory sensation with appropriate hearing aids. Table 1 lists the characteristics of the subjects, and Tables 2 and 3 list the aided (hearing aid) and unaided thresholds. The deaf children with tactile aids were matched as closely as possible to those who received a cochlear implant. No attempt to randomize the subjects was made because of strong treatment preferences, particularly among parents of children seeking cochlear implants. The groups of subjects were similar with respect to mean age at onset of deafness and the number of years between the onset of deafness and receipt of the sensory aid. The age at onset of deafness was slightly later for the users of the House 3M device. However, the subjects within each group showed large individual differences with respect to these variables. On the average, the users of the House 3M device received the implant when they were older and had used it for a longer period of time than the subjects in the other two groups.

METHODS

All subjects received the same intensive training with their devices. The training was initiated immediately after the fitting of the device (time of hookup for implant subjects) and continued through the first 6 months of device use. The training program consisted of a minimum of 30 hours of individual rehabilitation focusing on auditory, speech,

TABLE 3. UNAIDED PURE TONE THRESHOLDS (dB SPL)

Subject	*Ear*	*Frequency (Hz)* 250	500	1,000	2,000	3,000	4,000
Subjects with Tactaid II device							
1	R	105	120	NR	NR	NR	NR
	L	105	115	NR	NR	NR	NR
2	R	95	115	125	NR	NR	NR
	L	100	120	NR	NR	NR	NR
3	R	85	110	110	NR	NR	NR
	L	80	110	NR	NR	NR	NR
4	R	NR	NR	NR	NR	NR	NR
	L	NR	NR	NR	NR	NR	NR
5	R	NR	NR	NR	NR	NR	NR
	L	NR	120	NR	NR	NR	NR
6	R	90	100	NR	NR	NR	NR
	L	90	95	115	NR	NR	NR
7	R	95	NR	NR	NR	NR	NR
	L	100	NR	NR	NR	NR	NR
8	R	110	115	NR	NR	NR	NR
	L	110	115	NR	NR	NR	NR
9	R	85	110	115	NR	NR	NR
	L	85	110	115	NR	NR	NR
10	R	105	120	NR	NR	NR	NR
	L	105	120	NR	NR	NR	NR
11	R	100	105	NR	NR	NR	NR
	L	105	105	NR	NR	NR	NR
12	R	80	95	105	NR	NR	NR
	L	85	105	NR	NR	NR	NR
13	R	95	120	125	NR	120	110
	L	NR	110	110	110	105	100
14	R	80	105	115	NR	NR	NR
	L	90	115	NR	NR	NR	NR
Subjects with House 3M cochlear implant							
15	(R)	NR	NR	NR	NR	NR	NR
	L	NR	NR	NR	NR	NR	NR
16	(R)	NR	NR	NR	NR	NR	NR
	L	NR	NR	NR	NR	NR	NR
17	(R)	NR	NR	NR	NR	NR	NR
	L	NR	NR	NR	NR	NR	NR
18	(R)	NR	NR	NR	NR	NR	NR
	L	80	100	NR	NR	NR	NR
19	(L)	116	NR	NR	NR	NR	NR
	R	NR	NR	NR	NR	NR	NR
20	(L)	60	80	110	NR	NR	NR
	R	70	90	NR	NR	NR	NR
21	(L)	NR	NR	NR	NR	NR	NR
	R	NR	NR	NR	NR	NR	NR
Subjects with House 3M cochlear implant (cont'd)							
22	(L)	NR	NR	NR	NR	NR	NR
	R	NR	NR	NR	NR	NR	NR
23	(R)	NR	NR	NR	NR	NR	NR
	L	NR	NR	NR	NR	NR	NR
24	(L)	116	NR	NR	NR	NR	NR
	R	116	NR	NR	NR	NR	NR
25	(R)	100	NR	NR	NR	NR	NR
	L	100	105	110	NR	NR	NR
26	(R)	NR	NR	NR	NR	NR	NR
	L	126	NR	NR	NR	NR	NR
27	(R)	95	NR	NR	NR	NR	NR
	L	90	NR	NR	NR	NR	NR
28	(R)	NR	NR	NR	NR	NR	NR
	L	NR	NR	NR	NR	NR	NR
29	(L)	NR	NR	NR	NR	NR	NR
	R	NR	NR	NR	NR	NR	NR
30	(L)	NR	NR	NR	NR	NR	NR
	R	NR	NR	NR	NR	NR	NR
31	(R)	NR	NR	NR	NR	NR	NR
	L	NR	NR	NR	NR	NR	NR
32	(R)	NR	108	117	NR	NR	NR
	L	93	NR	NR	NR	NR	NR
Subjects with Nucleus 22-channel cochlear implant							
33	(R)	NR	NR	NR	NR	NR	NR
	L	NR	NR	NR	NR	NR	NR
34	(R)	90	NR	NR	NR	NR	NR
	L	95	110	NR	NR	NR	NR
35	(L)	NR	NR	NR	NR	NR	NR
	R	NR	NR	NR	NR	NR	NR
36	(L)	95	NR	NR	NR	NR	NR
	R	95	NR	NR	NR	NR	NR
37	(L)	NR	NR	NR	NR	NR	NR
	R	NR	NR	NR	NR	NR	NR
38	(L)	95	NR	NR	NR	NR	NR
	R	80	110	NR	NR	NR	NR
39	(R)	NR	NR	NR	NR	NR	NR
	L	NR	NR	NR	NR	NR	NR
40	(R)	75	90	115	NR	NR	NR
	L	65	95	NR	NR	NR	NR
41	(R)	NR	NR	NR	NR	NR	NR
	L	NR	NR	NR	NR	NR	NR
42	(L)	110	105	110	115	120	120
	R	105	105	115	150	120	120

Parentheses indicate ear later receiving implant.

NR — no response at audiometric limits.

and language needs of each child, and additional time was spent with the implant users for device setting and adjustment. This program was provided at the Indiana University School of Medicine for all implant subjects and for the tactile aid subjects within commuting distance and was coordinated with the programs in the child's school. The remainder of the children with tactile aids received their training from a rehabilitation specialist in their home city.

A battery of test procedures was used to assess the subjects' perception abilities. The tasks ranged from detection of sound to comprehension of connected discourse. Because standardized tests appropriate for very young and very deaf children were not available, several new measures were developed. The tests were administered to each subject in the preimplant or pre–tactile aid condition and at 6-month intervals thereafter.

Discrimination Test. The Change/No Change test[1] is designed to assess a child's ability to detect an acoustic change in a suprasegmental or segmental feature of speech. There are nine subtests, each of which consists of a particular contrast (eg, voiced versus voiceless). The trials in each subtest consist of ten syllables. For the No Change trials the ten stimuli are the same (ten ba's). For the Change trials, the last five stimuli differ from the first five (eg, bababababapapapapapa). This test was developed as an alternative to word recognition tasks, which are beyond the capabilities of many implant and tactile aid users. The paradigm is based on that used to assess the perceptual skills of infants, and has been used successfully with children from 5 to 10

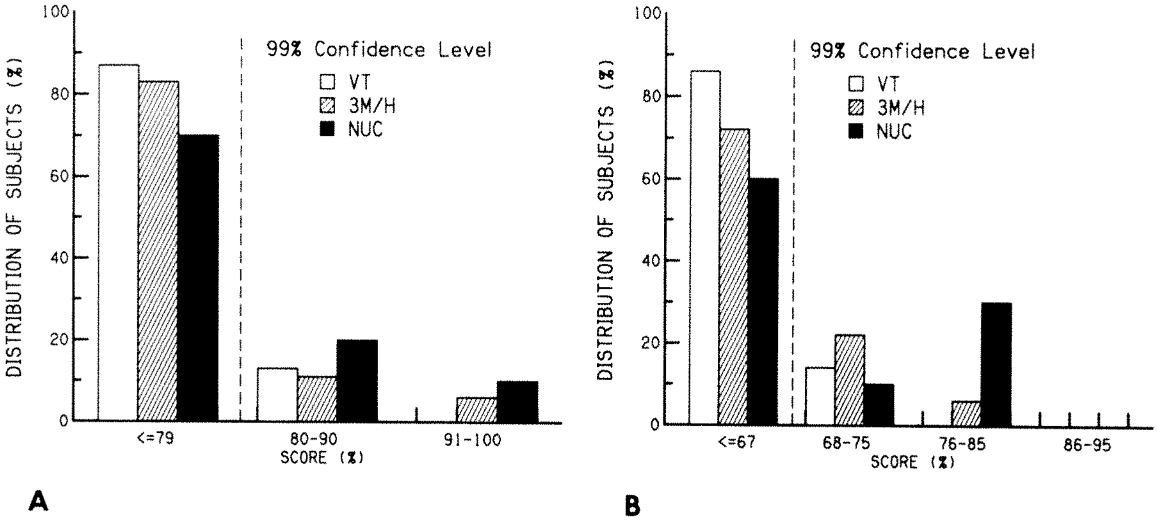

Fig 1. Percentage of subjects with each type of device who scored at or below chance (scores to left of dashed line) or significantly above chance (scores to right of dashed line). VT — vibrotactile device (Tactaid II), 3M/H — House 3M, NUC — Nucleus. A) Change/No Change test. B) Minimal Pairs test.

years of age.[2] The stimuli are spoken by an adult male, digitized, and manipulated so that each set of stimuli varies only with regard to the feature of interest.

Recognition Test. The Minimal Pairs test[3] is a two-alternative forced choice test that consists of pairs of pictured words that differ in one phonetic feature (eg, bear versus pear). The test consists of 20 pairs of words, with each pair differing in one of the following features: vowel height, vowel place, consonant manner, consonant voice, and consonant place. All items are presented in the auditory-alone condition. The child points to the picture corresponding to the word spoken by the examiner.

Speech Tracking. The ability of subjects to track connected discourse[4] was recorded in two conditions: lipreading alone, designated as device off; and lipreading plus device on. This task requires the child to repeat back verbatim passages of prepared text that are read by the examiner. Performance is expressed in terms of the number of words correctly repeated during a 5-minute interval in each condition.

RESULTS

Change/No Change Test. Because of the large individual differences among subjects within a group, the data are plotted in terms of the percentage of subjects who achieved a particular score on the test (Fig 1A). The score for each subject is the average of the scores on the nine subtests. The dashed line denotes a level of performance that is significantly above chance at the 99% confidence level, based on the normal approximation to the binomial distribution. Scores to the left of the dashed line are at or below chance, whereas scores to the right of the line are significantly above chance. Significant improvements were seen in some subjects with all three devices. However, more subjects with cochlear implants achieved high scores than did those with tactile aids. Of the cochlear implant subjects, more children using the Nucleus device achieved high scores than did those with the House 3M device.

Minimal Pairs Test. Again, the data are plotted in Fig 1B in terms of the percentage of subjects with each type of device who scored at or below chance or significantly above chance (as determined by the normal approximation to the binomial distribution). There is a trend for subjects with the Nucleus device to achieve higher scores than the users of the other two devices.

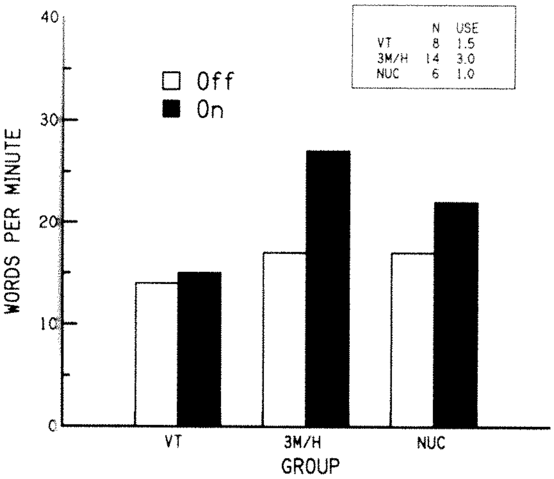

Fig 2. Mean tracking rates in words per minute for three groups of subjects in two conditions: device off (lipreading alone) and device on (lipreading plus device). VT —vibrotactile device (Tactaid II), 3M/H — House 3M, NUC — Nucleus, Use — mean number of years of use of device.

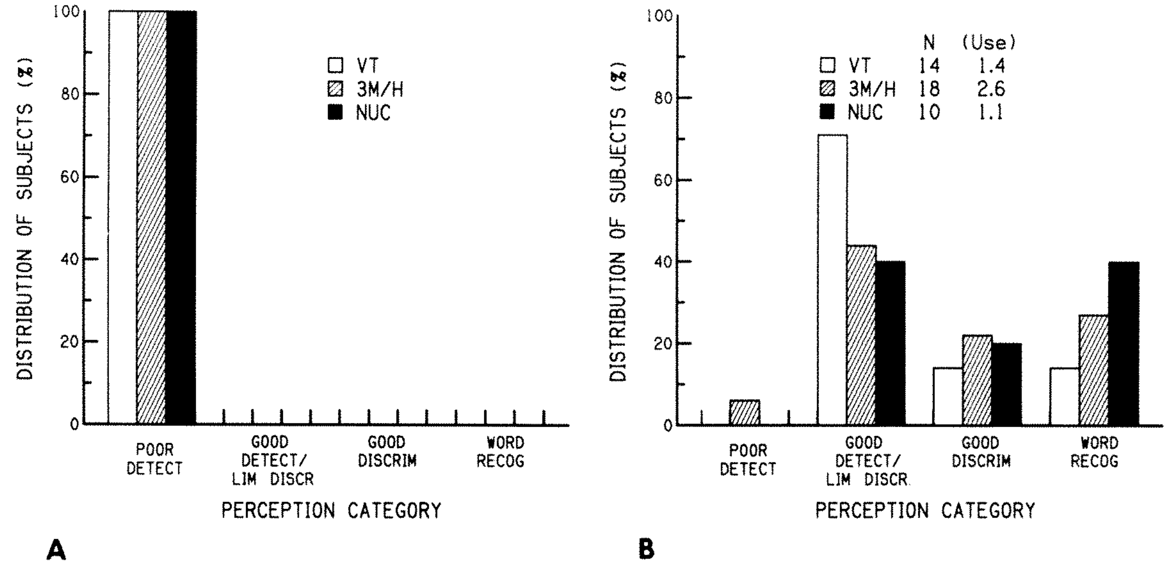

Fig 3. Categorization of subjects' perception abilities, based on warbled pure tone thresholds obtained in sound field and performance on Change/No Change test and Minimal Pairs test. A) While wearing conventional hearing aids. B) While using tactile aid or cochlear implant. VT — vibrotactile device (Tactaid II), 3M/H — House 3M, NUC — Nucleus, Use — mean number of years of use of device.

Speech Tracking. Data have been averaged across subjects in each group for the device-on and device-off conditions (Fig 2). The subjects in the two implant groups achieved higher tracking scores in the lipreading plus device-on condition than in the lipreading-alone condition. In contrast, little or no improvement in the tracking rate was observed in the device-on condition for the tactile aid subjects.

Perception Categories. A four-category classification scheme has been developed to describe the perception skills of the subjects. The criteria are based on the subject's performance on tests administered in the auditory-only condition. The child is classified as a "poor detector of sound" if aided warbletone thresholds in the sound field are greater than 60 dB hearing level (HL) at three or more frequencies. The next-highest category includes subjects who detected warbled pure tones at 60 dB HL and/or scored above chance on at least two subtests of the Change/No Change test, indicating good detection abilities, limited discrimination abilities, or both. Subjects who showed no evidence of word recognition skills but scored above chance on at least five subtests of the Change/No Change test are considered to have "good discrimination skills." Finally, subjects who scored above chance on the word recognition measures are placed in the highest category.

All subjects were poor detectors of sound while wearing conventional hearing aids prior to receiving either a tactile aid or a cochlear implant, as shown in Fig 3A. The percentages of subjects falling into each category after receiving a cochlear implant or tactile aid are demonstrated in Fig 3B. Four trends are demonstrated. First, with the exception of one subject with the House 3M device who remains a poor detector of sound, the performance of all subjects was improved with an implant or tactile aid as compared to a conventional hearing aid. Second, the majority of subjects with a tactile aid fell in the good detection/limited discrimination category, although a small percentage of them showed good discrimination abilities or evidence of word recognition. Third, roughly 40% of the subjects with each type of implant showed only good detection/limited discrimination skills. However, more subjects with implants were word recognizers than were the subjects with tactile aids. Fourth, the largest percentage of subjects who demonstrated word recognition abilities were among those using the Nucleus device.

SUMMARY AND CONCLUSIONS

Encouraging improvements were noted with all three devices. Higher levels of performance were documented with either cochlear implants or tactile aids than with conventional hearing aids for this population. Although large performance differences were seen with subjects using a particular device, both cochlear implant designs appear to offer advantages over the Tactaid II in providing ancillary speech perception cues to deaf children. This observation is consistent with results of comparative studies of deaf adults using the same devices.[5,6]

Preliminary observations suggest that the multichannel coding scheme may be superior to the single-channel cochlear implant design. Likewise, continued vibrotactile work is planned with a view toward implementing more sophisticated tactile devices as they become available.

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TELEPHONE SPEECH COMPREHENSION WITH USE OF THE NUCLEUS COCHLEAR IMPLANT

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The reported telephone usage by cochlear implant recipients has become a major issue of controversy. Although patients and clinicians report good communication skills via the telephone, no standardized tests have been used and no quantifiable results have been reported. In an effort to determine the extent to which our better-performing patients can use the telephone, we established a clinical protocol to assess their ability to recognize speech, taking into consideration the problems inherent in telephone testing. Eight cochlear implant recipients were administered the NU-6 Monosyllabic Word Test and the City University of New York Topic Related Sentences under the following listening conditions: soundfield in a soundproof suite and via telephone within the hospital, locally, and long-distance. Twenty-three percent of the patients implanted at New York University Medical Center demonstrated a significant degree of telephone communication ability.

KEY WORDS — cochlear implant, hearing, speech comprehension, telephone.

INTRODUCTION

The ability of some profoundly hearing-impaired individuals to communicate without the benefit of lipreading following multichannel cochlear implantation has been documented in the recent literature.[1,2] In addition, however, some of those patients, using one of the several multichannel cochlear implants, also have claimed an ability to carry on a telephone conversation without the benefit of a code. Although the majority of this reporting remains anecdotal, in 1985 Brown et al[3] tested one multichannel recipient in Australia with the telephone using Central Institute for the Deaf (CID) sentences. They found that the patient's performance averaged 21% correct with no repeat of stimulus, and 47% when the stimulus was repeated once. Cochlear Corporation sent out a questionnaire to 281 recipients of the Nucleus device. Fifty-one percent of the 146 respondents claimed that they could have an interactive telephone conversation either always or sometimes (J. Brimacombe, Cochlear Corporation; personal communication, 1989). The conclusion, however, of the National Institutes of Health Consensus Development Conference[4] panel in May 1988 was that not enough evidence was available to make a statement regarding telephone competence. Although many of our patients also have reported communication capability when using the telephone, they had never been tested formally. The purpose of this study was to attempt to evaluate the ability of our cochlear implant recipients to communicate via the telephone without benefit of a code.

METHODS

To date, 22 postlingually deafened adults have been implanted at New York University (NYU) Medical Center with the Nucleus multichannel cochlear implant. Eleven of these 22 patients (50%) had various degrees of open-set speech discrimination on routine postoperative evaluations. Their NU-6 scores ranged from 8% to 50%, and CID sentence scores from 8% to 100%. Although only six of these patients (27% of the 22 patients) reported an ability to have interactive telephone conversations, we decided to test as many patients as possible with any amount of open-set speech discrimination as evidenced on the CID sentence test; therefore, eight were subjects in this study (patients 9 through 11 were unable to participate for personal reasons). Patients 12 and 13, who did not have open-set speech discrimination on formal testing, were also included as subjects, since they reported being able to have conversations on the telephone (see Table).

Subjects were tested with a GSI 10 audiometer (Grason-Stadler, Inc) in a soundproof Industrial Acoustics Co suite (A); on extension telephones Bellevue to Bellevue (B); on a local call Bellevue to NYU Medical Center (C); and on an NYU-to-home call (D), which involved long-distance calling for four of the patients. The stimuli used were the NU-6 words and the City University of New York (CUNY) Topic Related Sentences,[5] all presented live voice. The stimuli were presented once with no repetitions, and the phone calls were made in a quiet but not sound-treated room. The CUNY sentences consist of 72 sets. Within each set of 12 sentences, there is a sentence relating to each of 12 topics: food, family, work, clothes, animals, home, sports/hobbies, weather, health, seasons/holidays, money, and music. The length of the utterance varies from

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POSTIMPLANTATION RESULTS

Patient	*NU-6 Score (%)*	*CID Score (%)*	*Reported Telephone Use*
1	48	89	Yes
2	20	21	No
3	40	67	Yes
4	30	87	Yes
5	8	8	No
6	32	82	Yes
7	16	36	No
8	50	100	Yes
9	20	61	Yes
10	12	38	No
11	16	37	No
12	0	0	Yes
13	0	0	Yes

three to 14 words, and declaratives, interrogatives, and imperatives are represented in each set. These sentences were chosen because of their lack of familiarity to the subjects.

The initiating telephone calls were all made on Northern Telecom equipment with use of Nynex lines for the local calls and AT&T for long-distance calls. The Bell system acceptable bandwidth for a voice signal is 200 to 3,500 Hz. The frequency response of the Bellevue telephone receiving the call was measured by use of a Fourier analysis, and the Bell system standards were met.[6] All subjects used standard acoustic coupling for testing purposes, ie, the telephone receiver was held up to the microphone headset.

There were four randomizations (trials) of each condition to ensure that an order effect was not present and to attempt to account for varying telephone transmission impairments. All subjects had been trained in telephone usage as part of their rehabilitation program. In addition, five normal-hearing adults were used as controls and were submitted to the same protocol.

RESULTS

Eight of the ten subjects completed the testing protocol. The remaining two patients (12 and 13) claimed to participate in telephone conversations at home, but it became clear at the initial stages of testing that they could not perform the task, and testing was discontinued.

All eight of the patients were able to recognize some stimuli over the telephone. The scores for the first eight patients under all of the conditions are shown in the Figure. The NU-6 words were scored as both percent words correct and percent phonemes correct. The mean of the four trials was used. Scores ranged from 2% to 63% on NU-6 words (words correct), from 7% to 74% on NU-6 words (phonemes correct), and from 3% to 99% on CUNY sentences.

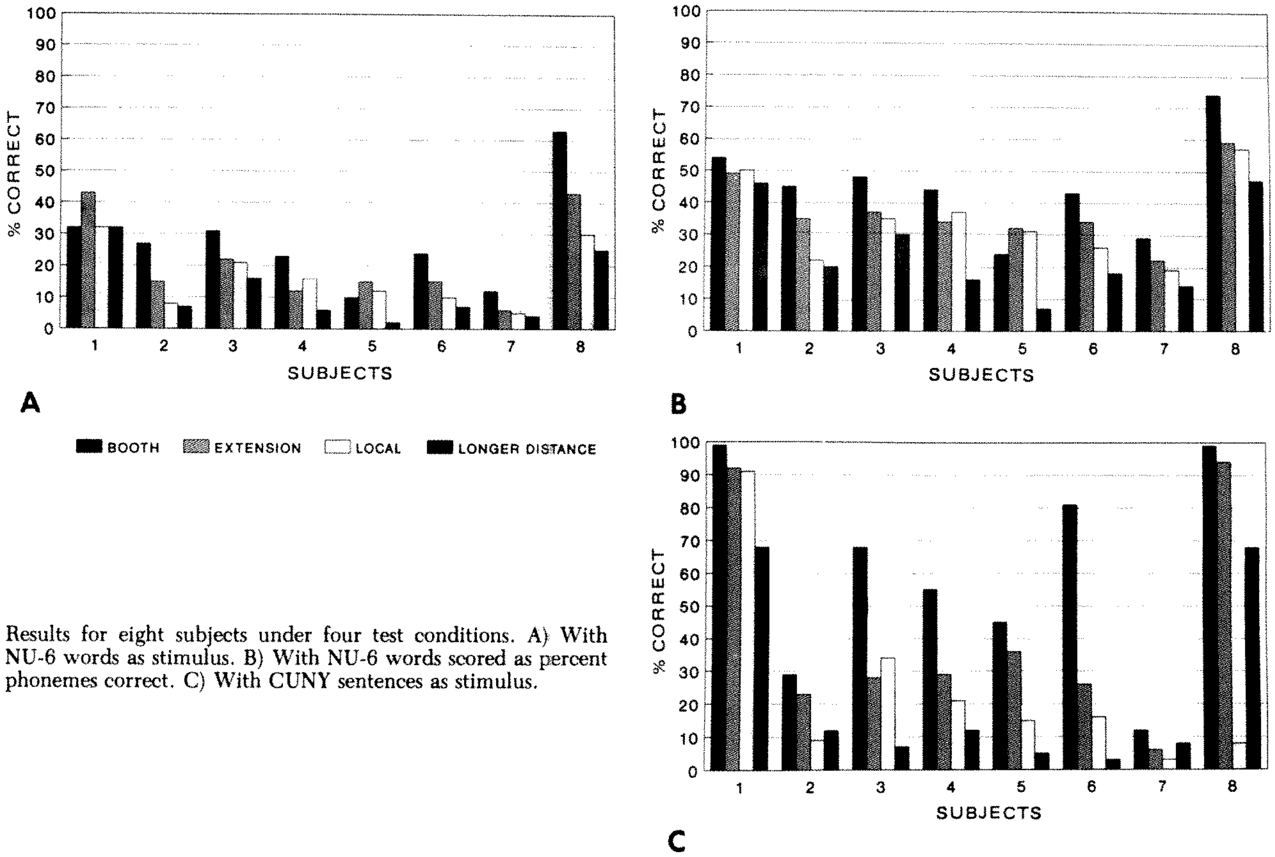
Analysis of data using the Mann-Whitney rank-sum test showed no significant difference ($p > .05$) among conditions B, C, and D when the NU-6 words were scored as words. When they were scored as phonemes, however, a significant difference ($p < .05$) existed between B and D and between C and D. No matter how they were scored (either as words or phonemes), a significant difference ($p < .05$) existed between A and D. For the CUNY sentence test, results were significant ($p < .05$) for A versus both C and D and between B and D. Overall, the farther the signal travelled, the poorer the results. In addition, there was a significant difference ($p < .05$) in the overall performance of the patients on the CUNY sentences versus the NU-6 words scored as percent words correct across all telephone conditions. For the normal-hearing subjects, no significant differences were found for any of the conditions with either stimulus.

Although our data show that all eight subjects had some amount of open-set speech recognition on the telephone, only five reported actually being able to communicate in an interactive fashion on the telephone at home or at work. These same five subjects, on routine postimplant testing, had CID sentence test scores (sound only) of 50% or greater. This correlates with the scores obtained for the CUNY sentences when presented through the audiometer. The scores for the remaining three subjects were below 50% for both of the sentence tests, namely 8%, 21%, and 35%, respectively. These subjects report that they are unable to communicate effectively on the telephone.

DISCUSSION

It appears from the results of this study that a 50% or greater score on CID sentences presented sound only is a good indicator of telephone competence. This number is in agreement with the findings of Johnson and Rubenstein,[7] who stated that one of the prerequisites for possible two-way telephone usage for hearing-impaired students at the National Technical Institute for the Deaf (Rochester, NY) was a 50% score on the CID sentence test. In contrast, Brown et al[3] found that the patient they tested had a CID score of 38% during conventional testing and was able to use the telephone effectively.

Although all eight of our subjects had some amount of open-set speech recognition both on CID sentences (during routine follow-up testing) and on the stimuli used in this study, only five of them (23% of our total implanted adult population) can and do use the telephone effectively. If we apply the 50% cutoff to the three patients who could not participate in this study, we could add one patient to the total who do use the phone, and the percentage would increase to 27%. Indeed, this one patient reports being able to use the telephone effectively



Results for eight subjects under four test conditions. A) With NU-6 words as stimulus. B) With NU-6 words scored as percent phonemes correct. C) With CUNY sentences as stimulus.

sometimes, while the remaining two patients with CID scores of less than 50% do not.

There are many other factors, however, that need to be considered when telephone competence is discussed. Although the performance of normal-hearing people appears not to be adversely affected by the transmission of stimuli such as the NU-6 words or CUNY sentences over the telephone, that of cochlear implant recipients clearly is. One would have to anticipate that with the addition of transmission impairments on digital circuits such as amplitude and frequency distortion, circuit noise, and intelligible cross talk, and, on long-distance lines, talker echo and delay, their abilities would be compromised further. Transmission impairments such as impulse noise and linear and nonlinear distortion over analog systems need to be considered as well.[6]

Another issue is the willingness of the patient to expend both the physical and mental energy required to control the environment. All of the five patients who consistently use the telephone report attempting to manipulate the conversation so that they can effectively control both the context and the possible responses. It is not surprising that these subjects performed better on the sentence test, because of the contextual clues available to them with these stimuli. They are also not shy about requesting as many repetitions and rephrasings as they need. It is possible that some additional patients who have some open-set speech recognition could use the telephone in some limited conditions if they were more motivated to do so. But they believe that the ultimate benefits do not outweigh the level of effort they must apply to the task, they fear embarrassment, and they do not believe that their conversations are interactive. They can, however, understand some material on the telephone, as evidenced by our results. Should they, therefore, be considered as patients who can use the telephone to a limited degree? If so, then the percentage of our patients who can perform the task increases to 50%. This would correspond more closely with the results of the Cochlear Corporation patient questionnaire, in which 51% of the patients reported telephone competence.

It is evident, however, that a patient's reported telephone ability does not always reflect actual competence (two subjects in our study), and some type of assessment and judgment should be made by the clinician. This also would assist in making decisions as to who might benefit from extensive telephone training, such as those patients who have some open-set speech recognition and are properly motivated. They may benefit from increased training and learn to use the telephone in some limited fashion.

CONCLUSIONS

Twenty-three percent of the patients implanted at NYU Medical Center with the Nucleus multichannel cochlear implant have demonstrated a significant degree of telephone communication ability. Fifty percent have a very limited ability to discriminate some speech sounds on the telephone. A postoperative CID sentence test score of 50% or more appears to be a good predictor of usable telephone skills. This may serve as a guide to postoperative telephone-usage training.

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AUDIOLOGIC RESULTS FOLLOWING REIMPLANTATION OF COCHLEAR IMPLANTS

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Five patients using cochlear implants experienced internal device failure 6 weeks to 4 years following implantation. All devices were removed and new electrodes inserted. Single-channel implants were replaced with multichannel systems in three patients, while the others received identical multichannel implants. The performance on a uniform battery of audiologic tests was the same or better with the second implant in all patients. Replacement of intracochlear electrodes did not induce clinically apparent degeneration of auditory performance in this series.

KEY WORDS — cochlear implant, reimplantation.

INTRODUCTION

A frequent question of candidates seeking a cochlear implant is whether the internal components of the device can be changed or upgraded in the future. During the developmental history of cochlear implants, internal device failure has not been uncommon. Several subjects have had original implants replaced with similar systems. Most of these cases involved single-wire intracochlear electrodes. There have been a few reports of replacement of longer multichannel electrodes[1] and two reports of changing a single-channel system to a multichannel design.[2,3] In most instances the performance reported with the replacement device was similar to or better than that with the original. Even though the present generation of implanted components appears stable, rapidly advancing technology may soon render it outmoded. Multichannel implant systems have been shown to provide enhanced speechreading, sound awareness, and word understanding compared to single-channel designs.[4] Inquiries regarding upgrading from single-channel to multichannel implants are beginning to occur and likely will increase.

Intracochlear damage from electrode placement always has been a concern of cochlear implant developers. Reimplantation compounds such concerns. A preliminary study in monkeys by Miller et al[5] suggests that reimplantation induced significant degeneration of spiral ganglion cells in the apex of the cochlea.

In light of these findings and the limited performance data regarding replacement of cochlear implants, five case histories from patients undergoing reimplantation for original device failure are described. This report does not address the issue of intracochlear damage, but carefully compares the performance characteristics with the original and replacement devices on similar audiologic measures.

MATERIALS AND METHODS

Four postlingually deafened adults and one perilingually deafened adolescent experienced device failure 6 weeks to 4 years following placement of their original implants. The four adults had undergone extensive audiologic evaluation with their devices prior to failure. The adolescent patient was not tested at our center prior to device failure.

Audiologic performance was measured with the Iowa cochlear implant battery, which consists of selected tests from the Minimal Auditory Capabilities Battery (MAC)[6] and others developed at the University of Iowa.[7,8] These tests document the ability of implant subjects to recognize environmental sounds, identify speech in noise (Spondee Four-Choice Quiet/Noise), augment speechreading (Sentence Test Without Context–Vision and Sound), and identify speech in the sound-only condition (Sentence Test Without Context–Sound Only and NU-6 Monosyllabic Word Test).

All tests were presented in a sound field at 65 dB sound pressure level (SPL). Patients were encouraged to adjust their speech processors to the most comfortable level (MCL). Test materials were recorded on audiotape, videotape, or laser videodisc. Speakers were unfamiliar to the patients, and only one presentation of an item was given. Open set refers to unfamiliar sound or speech material presented without multiple choice response constraints. None of the test material was used for rehabilitation.

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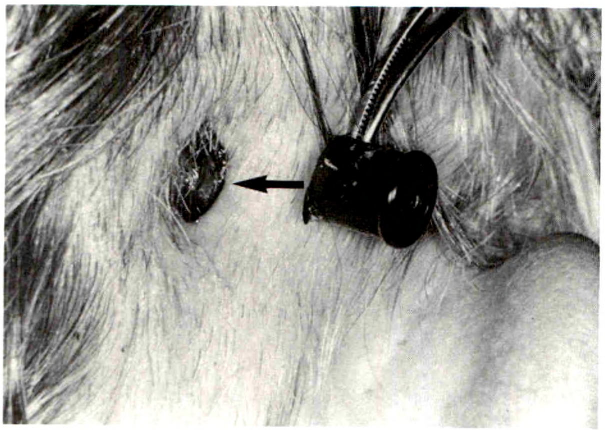

Fig 1. (Patient 4) Fractured pedestal from base (arrow) of percutaneous plug.

Psychophysical testing was performed on two patients using their original and replacement implants. Measures obtained by passing stimuli through the patients' processors included thresholds, MCLs, gap detection, and frequency difference limens.[9] Test methods have been described elsewhere.[9]

CASE REPORTS

Patient 1. Patient 1 was deafened at age 43 as a result of bilateral temporal bone fractures. A House Sigma 7 single-channel system was implanted by another implant team 7 years later. He began to experience intermittent function after using the implant for 3 years, and the device failed to stimulate 6 months later. In December 1984 the House electrode was removed and a Nucleus (Cochlear Corporation) intracochlear system was inserted. The House Sigma 7 electrode was found to be in place 16 mm within the scala tympani and had been placed through the round window. There was scarring around the electrode within the mastoid, but the facial recess and middle ear were free of scar tissue. The electrode was easily withdrawn to the level of the round window. At this point some resistance was encountered. The round window was opened to allow removal of the electrode. A cochleostomy was created anterior and inferior to the round window membrane with a 0.7-mm diamond bur. The Nucleus electrode was inserted through the cochleostomy without resistance or other difficulty.

Patient 2. A 57-year-old woman began to experience fluctuating hearing loss and vertigo at 27 years of age. A diagnosis of congenital syphilis was made and she received appropriate antibiotic therapy. By 40 years of age her progressive hearing loss became bilaterally profound, and her hearing was unresponsive to the limits of the audiometer. She was implanted at 53 years of age with a Hochmair/Vienna intracochlear single-channel implant. The original electrode was placed 23 mm into the scala tympani through a cochleostomy. The device failed 4 years later. The Vienna electrode was removed and replaced with a Nucleus multichannel system in July 1987. Dense scar tissue surrounded the electrode in the mastoid, but the round window region was identified easily through the facial recess. The original electrode was removed without resistance. The fascia placed around the cochleostomy at the first procedure was removed with instrumentation, and the new electrode placed through the same cochleostomy. A full 24-mm insertion into the scala tympani was achieved without difficulty.

Patient 3. Patient 3 was profoundly deafened at 6 years of age following *Hemophilus influenzae* meningitis. She received a House 3M Alpha implant system at age 14 at another hospital. The original device failed to stimulate 2$^1/_2$ years later. A Nucleus multichannel system was placed following removal of the House implant at age 17. The House ball electrode was found to be embedded in scar tissue at the round window. The electrode was removed without leakage of perilymph from the scala tympani. A cochleostomy was created anterior and inferior to the round window, and the Nucleus electrode was advanced 24 mm into the scala tympani without resistance.

Patient 4. A 69-year-old man was in good health until he fell from a roof, sustaining bilateral temporal bone fractures. He had aidable hearing in the right ear for 2 months postinjury, but it deteriorated rapidly.

One year following the accident, an Inneraid (Symbion Inc) multichannel implant was implanted in the right ear. Eighteen months later he struck his head on the door frame of his car, causing a fracture of the percutaneous pedestal from the base (Fig 1). During removal of the original electrode, new bone growth at the cochleostomy site was encountered. A drill was required to remove the bone around the electrode. A small amount of fibrous tissue also was removed within the basilar turn. A new pedestal and electrode were placed. The replacement electrode was inserted fully into the scala tympani. A small amount of granulation tissue was found under the original pedestal. The infected area did not extend beyond the base and did not involve the electrode. The granulation tissue was debrided thoroughly prior to securement of the new pedestal. Postoperative antibiotics were administered, preventing further infection.

Patient 5. Patient 5 was involved in a motor vehicle accident at age 26, resulting in multiple injuries including a transverse temporal bone fracture of the right ear. During his hospitalization, high dose aminoglycoside therapy was required, resulting in profound loss of hearing in both ears. A Nucleus multichannel implant was placed in the left ear 1 year following the accident. Six weeks after

TABLE 1. PERCENT CORRECT ON IOWA EVERYDAY SOUNDS TEST

	Original Implant		*Replacement Implant*	
Patient	*Type*	*Score*	*Type*	*Score*
1	House	25%	Nucleus	30%
2	Vienna	40%	Nucleus	44%
4	Symbion	41%	Symbion	41%
5	Nucleus	38%	Nucleus	66%

connection of the speech processor, the internal electrode failed to stimulate. A second Nucleus multichannel implant was placed in the same ear. Upon removal of the original electrode, a small amount of fibrous tissue was seen in the basilar turn. The tissue was removed, and the new device placed 24 mm into the scala tympani.

RESULTS

All five patients were able to hear sound with their replacement implants. The two patients with failed multichannel implants (patients 4 and 5) stated that the new multichannel implants restored a similar or slightly better auditory sensation than the original. They did not experience any regression in their ability to recognize familiar sounds and speech. The other patients were changed from single-channel to multichannel processing. Their initial experience with the multichannel device was confusing, similar to the first time they heard electrically processed sound. With time, all said the multichannel implant delivered "more speechlike sound" than their single-channel implants.

The audiologic performance on selected tests from the Iowa cochlear implant battery with the original and replacement devices is presented in Tables 1 and 2 and Fig 2. The scores were obtained after 1 year or more of experience with the original device (except for patient 5) and 1 year of experience with the replacement. Results with the original implant for patient 5 were obtained at 1 month. His device failed shortly after the testing.

TABLE 2. SPEECHREADING ENHANCEMENT AS TESTED BY PERCENT CORRECT ON IOWA SENTENCE TEST WITHOUT CONTEXT

		Sound and Vision With Original Implant		*Sound and Vision With Replacement Implant*	
Patient	*Vision Only*	*Type*	*Score*	*Type*	*Score*
1	26%	House	45%	Nucleus	50%
2	30%	Vienna	50%	Nucleus	94%
3	43%	NA		Nucleus	79%
4	0%	Symbion	67%	Symbion	76%
5	10%	Nucleus	92%	Nucleus	98%

NA — not applicable.

The ability to recognize environmental sounds (Table 1) was not altered in any of the patients by changing devices. Multichannel processing did not allow patient 1 or patient 2 to identify any more environmental cues than did single-channel systems. The improvement from 38% to 66% for patient 5 could be attributed to learning, since most patients improve during the first year of implant use. These results are similar to those of a group of subjects tested on the Everyday Sounds test using the Nucleus implant (n = 18, average score = 43%) and Symbion implant (n = 19, average score = 53%).[4]

Enhancement of speechreading was measured with the Iowa Sentence Test Without Context, first in a vision-only condition and then in a speech-processor-plus-vision condition. Table 2 presents the results. All patients achieved speechreading enhancement with their devices. Changing to a multichannel implant was a substantial benefit to patient 2, while patient 1's score was similar to that with the original single-channel implant. The multichannel subjects (patients 4 and 5) showed little change.

Another very important measure of performance is the ability to understand speech without the aid of speechreading. The Iowa Sentence Test Without Context (Fig 2A) and the NU-6 Monosyllabic Word Test (Fig 2B) presented in a sound-only condition

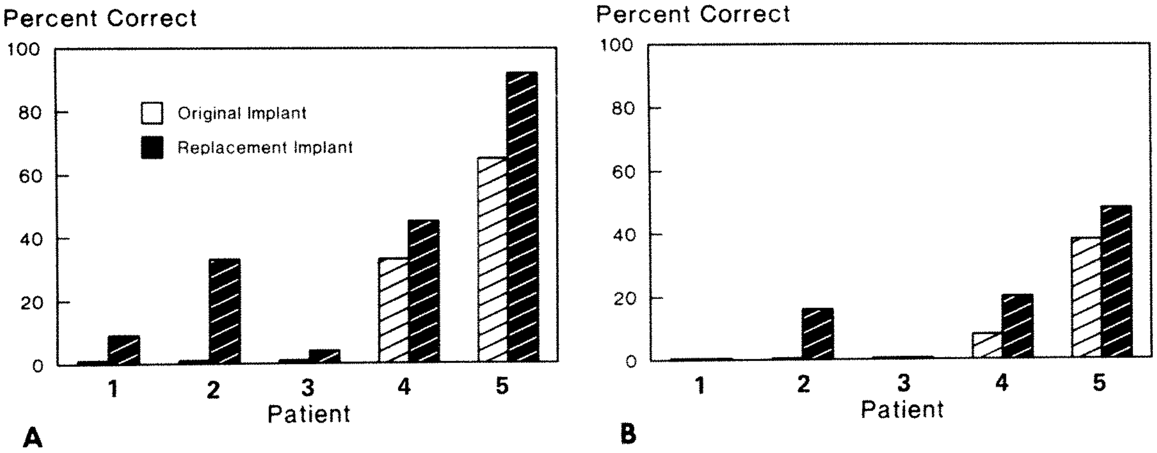

Fig 2. Performance scores. Original device for patients 1, 2, and 3 was single-channel implant. Replacement implant was multichannel for all patients. A) Iowa Sentence Test Without Context in sound-only condition. B) NU-6 Monosyllabic Word Test.

are used to measure speech understanding. All patients did better on the sentence test with the replacement devices (Fig 2A). A wide range of scores on this test (0% to 92% correct) was found when 37 other patients using multichannel implants were evaluated.[4] The average score for the 37 patients was 31% (Nucleus n = 18, 32%; Symbion n = 19, 30%). In contrast, only one of 15 single-channel implant users was able to identify any of the words, and that patient scored 3%. Changing to a multichannel system was beneficial to all three patients. Changing multichannel devices was not detrimental to patient 4 or patient 5. They have continued to make modest gains over time.

Scores on the NU-6 Monosyllabic Word Test also improved for four patients. Word recognition results are seen in Fig 2B. Patient 3 was unable to recognize any words, but did identify 12% of the phonemes presented. Patient 1, on the other hand, was still unable to recognize any words or phonemes on this test. Phoneme recognition scores were 38% for patient 2, 24% for patient 4, and 60% for patient 5 with the replacement implants.

Two patients (4 and 5) have undergone additional psychophysical evaluations with both their original and replacement multichannel implants. Patient 4 exhibited a gap detection of 5 ms at MCL with the original implant and 6 ms with the second implant. The gap detection for patient 5 was 7 ms with the original implant and 5 ms with the replacement. The voicing frequency difference limens, thresholds, and MCLs measured through the processor were unchanged or slightly improved with the replacement systems for both patients.

DISCUSSION

Replacement of failed intracochlear electrodes was successful in restoring hearing in all five patients in this series. It was possible to remove the House Sigma 7, House 3M Alpha, Vienna intracochlear bipolar, Nucleus, and Symbion electrodes and replace them with similar or different configurations. It had been suspected that replacement of electrodes would be difficult because of intracochlear scarring or bone growth, and that these problems would be compounded with placement of longer and larger-diameter electrodes. This was not our experience. Only one device change required removal of new bone growth in the basilar turn, and this had no detrimental effect on performance. Fibrous tissue was encountered in the basilar turn in two cases. However, it was removed easily. All replacement electrodes were inserted into the scala tympani to their designed depth.

The only difficulty encountered in all cases was the dense scar surrounding the electrode in the mastoid, which was minor. Careful dissection is required to free the electrode. In two cases new mastoid cortical bone surrounded the wires.

A significant finding in this series was that the audiologic performance did not deteriorate in any of our patients. In addition, psychophysical measures in two patients indicate that changing long intracochlear electrodes does not induce progressive neural deterioration that is clinically apparent. The results reported were obtained 1 year after replacement of the device. Subsequent test results at 2 years and 3 years in patients 1 and 4 were unchanged.

The important issue of upgrading from single-channel to multichannel speech processing cannot be answered in a small series of cases. Nevertheless, patient 2 received substantial improvement in word understanding scores with the Nucleus implant compared to the Vienna single-channel design. Patient 1, in contrast, only experienced a minor enhancement on the sentence test and speechreading ability, when changed from a House to a Nucleus multichannel implant. Patient 3, the perilingually deafened subject, also had limited word understanding with the Nucleus multichannel implant. She was unable to recognize words in the sound-only condition with the House 3M Alpha implant on other tests.

A wide spectrum of performance levels has been seen with all implant types. Investigators have been unable to identify critical parameters that are necessary to achieve word understanding with a cochlear implant. Multichannel implant users recognize more speech than those who wear single-channel systems, but predicting preoperatively how an individual will perform has proven difficult.[4] A combination of cochlear nerve survival, implant design, and cognitive processing ability is thought to be important for word understanding. A recently developed technique of recording the whole nerve action potential of the auditory nerve may be a helpful future predictive aid.[10] Preliminary results from subjects with multichannel implants suggest that the refractory characteristics of the auditory nerve are predictive of the ability to process electrically coded speech signals. Until methods are developed to accurately predict performance, subjects must be informed that a change to a multichannel implant may not improve their perceptual skills. Removal of a functioning single-channel device in order to upgrade to a more advanced system is an individual decision. However, a more prudent approach may be to implant the unused ear. There are several supporting arguments for this point of view. First, the new system may not significantly enhance auditory perception, as occurred in one of our patients. Second, binaural electrical stimulation may be better than unilateral stimulation. Finally, electrical stimulation of the unused ear may prevent further neural degeneration, as suggested in a recent animal study,[11] and therefore be potentially beneficial to future implant systems.

This report does not address the question of whether changing intracochlear electrodes induces isolated auditory nerve degeneration. Further animal research is necessary to document whether these changes occur. Such changes may be important as more advanced implant systems are developed. However, the clinical significance of the changes also must be determined.

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HUMAN TEMPORAL BONE RESEARCH WORKSHOP REPORT

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LARYNGOLOGY

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This Workshop was held July 14-15, 1988, in Bethesda, Maryland, and was sponsored by the Deafness Research Foundation and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS). Publication of this supplement was made possible by a grant from the National Institute on Deafness and Other Communication Disorders (NIDCD)

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INTRODUCTION

The need for a Workshop of this nature stems from the perceived concerns of the scientific community and of its surrogates such as the National Institute on Deafness and Other Communication Disorders and the Deafness Research Foundation in the following areas related to human temporal bone research: 1) a decreasing interest by the scientific community in this area of research, 2) a decreasing number of physicians/scientists interested in human temporal bone research, 3) an impression that "cutting edge" methods are not being used currently in the United States, 4) a lack of hypothesis testing in research as opposed to the current methods of descriptive research, and 5) a lack of training of new temporal bone pathologists who will devote part or all of their careers to human temporal bone research.

In order to determine if these are real concerns, the goals of this Workshop were the following: 1) to present the state of the art of human temporal bone research and 2) to determine if problems exist, and if so, define them.

Finally, the Workshop conferees determined the future goals related to 1) techniques, 2) national and international coordination of collection of studies, 3) methods to stimulate interest in temporal bone disease, 4) training, and 5) potential areas of future research for which human temporal bones will be invaluable.

Charles D. Bluestone, MD

SPECIAL REMARKS

STUDIES OF TEMPORAL BONE HISTOPATHOLOGY IN HUMANS

We have seen numerous spectacular advances in otologic practice in recent years; nevertheless, there remain many otopathologic problems whose causes are unknown or uncertain. Solutions to many of these problems could come from disciplined histologic studies of the human temporal bone and central auditory structures, but interest in such studies appears to be waning among both otolaryngologists and pathologists.

Total National Institute on Deafness and Other Communication Disorders grant support for studies in this area, shared by a total of five investigators, amounts to less than $1 million, a fraction of 1% of the NIDCD budget, while support for studies of otitis media is close to $6 million. The most recent volume (vol 98) of *Otolaryngology-Head and Neck Surgery* carried only one article on human temporal bone disease, a report of colon cancer metastasis to the temporal bone. And in the past several years there have been no applications for Clinical Investigator Development Awards from young clinicians seeking training in temporal bone histopathology.

The explanations for this disturbing state of affairs in what used to be a flourishing area of research interest and productivity are clearly numerous and complex. Autopsy rates are down in many institutions; this is probably part of a general move toward cost containment, but there is also a widely held perception that noninvasive diagnostic studies have progressed to such a point that autopsies can have little more to add. There are also signs of a belief that the inner ear already has been studied in such exhaustive detail that nothing further of value can come from additional study. And no discussion of diminishing interest in temporal bone research could be complete without reference to the very familiar and widespread diminution of research involvement evidenced by surgeons generally, in itself the result of many interacting societal pressures and influences.

Recognizing the continuing importance of temporal bone studies to the care of our patients and the health of our specialty, this Workshop was convened under the joint auspices of the Deafness Research Foundation and the NIDCD to determine the nature of the problem(s) and to identify feasible and appropriate remedies.

Ralph F. Naunton, MD

HISTORICAL ASPECTS

EARLY HISTOPATHOLOGIC STUDIES OF EAR DISEASE AND DEAFNESS

JOSEPH E. HAWKINS, PHD, DSC

Supported by United States Public Health Service grant NS 21440 and Food and Drug Administration contract 223-87-6028.

INTRODUCTION

Histopathologic study of the inner ear came into its own as recently as the last decades of the 19th century. Doubtless it was inspired, at least in part, by the midcentury discoveries of Alfonso Corti[1] (1822-1876) and of the other anatomists whose names remain firmly affixed to the unique structures of the membranous labyrinth. Rudolf Virchow's founding of his *Archiv* (1847), with its emphasis on the importance of microscopy and the cell theory for the understanding of pathologic processes,[2] and his publication of *Die Cellularpathologie*[3] a few years later must have lent additional impetus, even though the book contains only a few lines about the ear itself. Progress in otopathology still had to await the development of appropriate histologic methods and the establishment of otology as an academic discipline.

Histology itself properly may be said to have had its dawn in 17th-century Bologna, with Marcello Malpighi (1628-1694) and his use of the microscope to study the pulmonary capillaries, the renal glomeruli, and the layers of the skin. Histologic technique came later. It was developed throughout the 19th century by the efforts of Johannes Evangelista Purkinje, Jacob Henle, Wilhelm His, Max Schultze, and other justly famous microanatomists. Thanks to their earlier work, the three decades from 1875 to 1905 deserve to be called "the first golden age of histological technique."[4] Summaries of 19th-century progress in microscopy and in microanatomic methods, which later paved the way for steady advances in otopathology, are to be found in Esmond Long's *History of Pathology*[5] and in the standard histories of medicine.

The membranous labyrinth was examined at first by microdissection, and its tissues as whole-mounts or surface preparations, since the special techniques required to prepare sections of the petrous bone and its delicate contents for microscopic examination were not available.

BEGINNINGS OF OTOPATHOLOGY IN PADUA AND LONDON

Morgagni. The first tentative otopathologic observa-

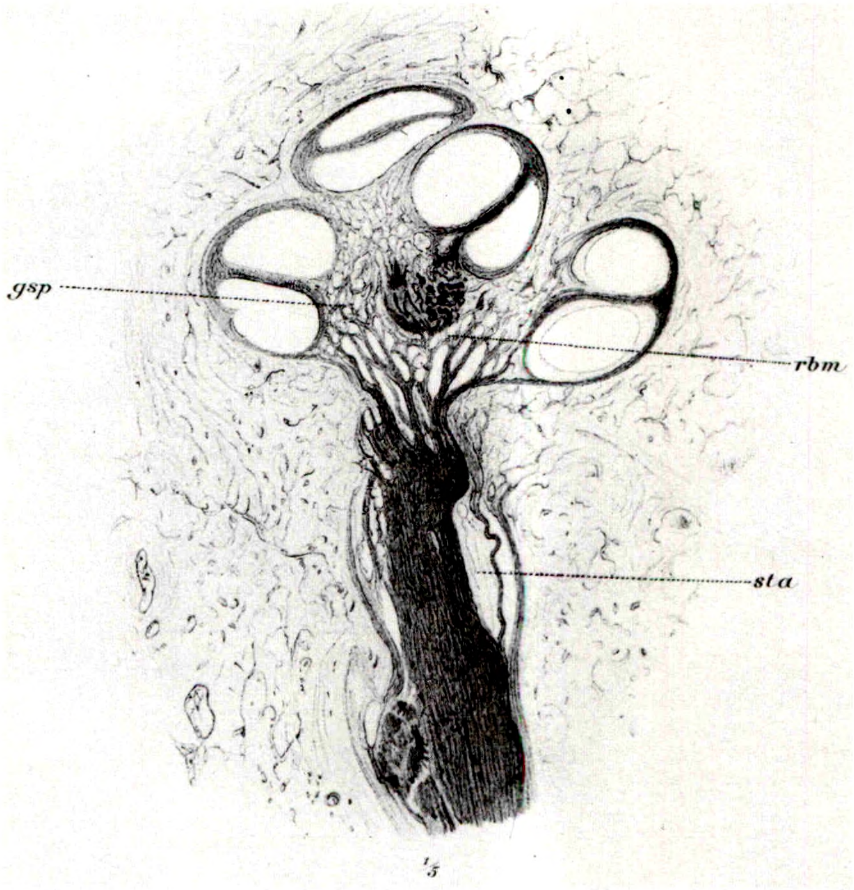

Fig 1. First published lithograph of midmodiolar section of cochlea, indicative of state of art of cochlear histopathology a century ago. Figure was intended to show degeneration of cochlear nerve fibers (sta), attributed to hemorrhage, in child who had died of diphtheria. Nerve fibers in modiolus (rbm) and spiral ganglion cells (gsp) were considered to be normal. Author did not comment on conditions in cochlea, in which severe postmortem autolysis had apparently caused almost complete disappearance of Corti's organ. (From Moos [1887].[19])

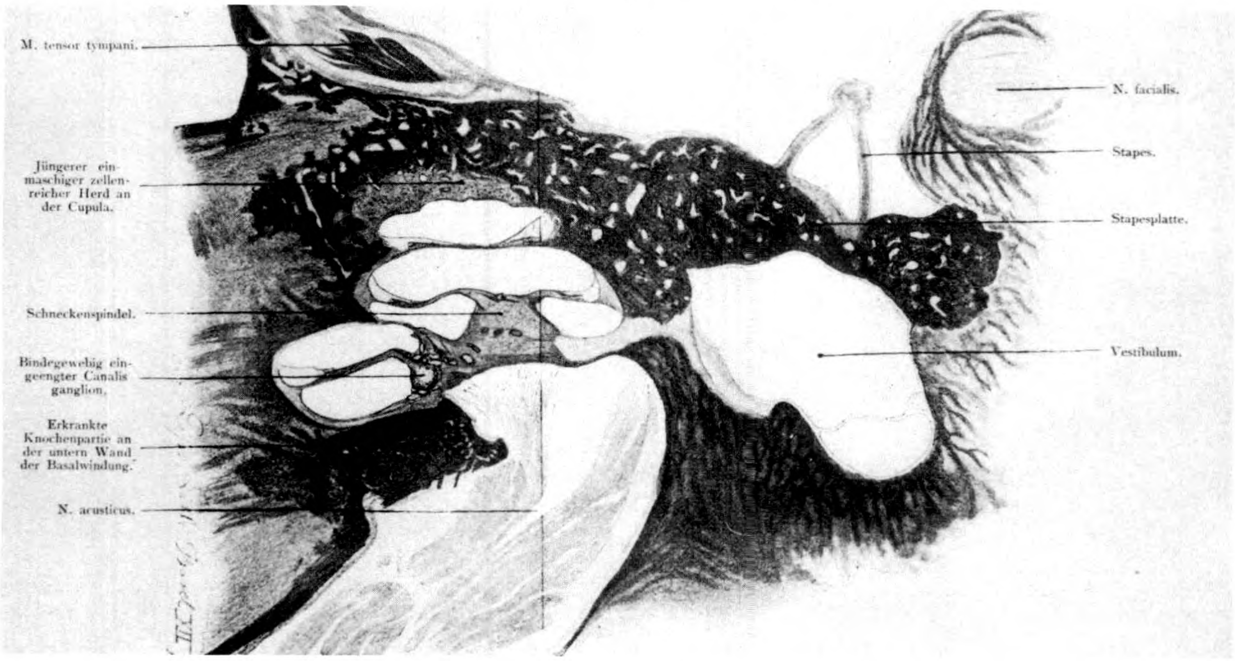
M. tensor tympani.
Jüngerer einmaschiger zellenreicher Herd an der Cupula.
Schneckenspindel.
Bindegewebig eingeengter Canalis ganglion.
Erkrankte Knochenpartie an der untern Wand der Basalwindung.
N. acusticus.
N. facialis.
Stapes.
Stapesplatte.
Vestibulum.

Fig 2. Horizontal section through right temporal bone of patient with extensive capsular otosclerosis and stapes ankylosis. During processing, specimen had been distorted by accidental compression after decalcification. State of preservation of Corti's organ represents combined effects of fixation and other histopathologic techniques. Between 1887 and 1898, techniques had improved, but results were still imperfect, especially for organ of Corti. (From Hartmann [1898].[25])

tions had been made in the course of anatomic dissections. An honored place as one of the earliest contributors to knowledge of the diseases of the ear is rightfully reserved for the founding father of morbid anatomy, Giovanni Battista Morgagni of Padua (1682-1771), pupil of Valsalva and teacher of Cotugno and Scarpa.[6] Letter XIV of his *De Sedibus, et Causis Morborum*[7] is concerned with the diseases of the ear and the nose. There he mentions, among other causes of deafness, ankylosis of the stapes and lues venerea. Also included is his discussion of the relation between labyrinthitis and cerebral abscess. Opposing the firm conviction of most of his contemporaries and of many of his successors, he argues that where both conditions are present, the primary infection is in the ear rather than in the brain.

Toynbee. Morgagni's influence as anatomist, physician, and savant was great and far-reaching, but it was not sufficient to convince his successors that the diseases of the ear could be respectable subjects for the attention of serious men of medicine and science. There was much inertia and prejudice still to be overcome, as witness the concern of Joseph Toynbee[8] of London and of Anton von Tröltsch[9] of Würzburg about the low esteem in which aural surgery was held by other medical men, not always without reason. In Britain as on the Continent, this undeveloped field, shunned by all but a few able practitioners, had become a lucrative playground enjoyed mainly by incompetents and charlatans.[10] In 1837 Toynbee (1815-1866), while still a medical student, announced his determination to "rescue aural surgery from the hands of quacks."[10] In his effort to

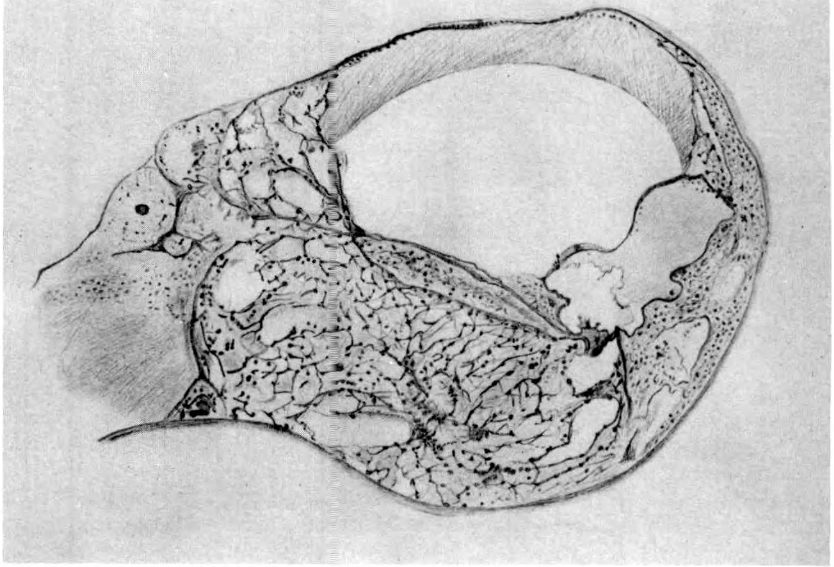

Fig 3. Fibrotic mass filling scala tympani (basal turn) in right ear of 35-year-old patient who had had lues for many years. (From Manasse [1901].[28])

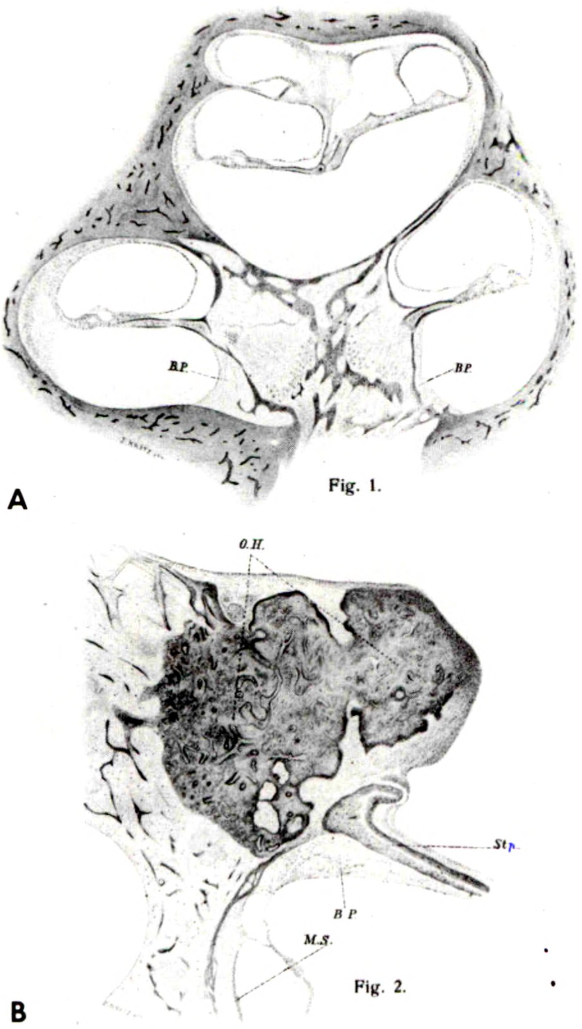

Fig 4. A) Nerve deafness in 77-year-old woman, attributed to typhus 30 years earlier. Manasse calls attention to remarkable dilatation of cochlear duct, indicated by position of Reissner's membrane; good preservation of Corti's organ, which was least affected; extensive loss of cells from spiral ganglion, especially in basal turn; and layer of connective tissue (BP) on medial wall of scala tympani. B) Otosclerotic focus at margin of oval window, unrelated to nerve deafness following typhus. (From Manasse [1909].[29])

establish a scientific basis for the study of aural diseases, he became the first ear surgeon to devote himself also to otopathology. By 1857 his series of temporal bone dissections numbered more than 1,600. Among them he chose some 800 specimens illustrative of various ear diseases to form the collection of which he published a catalogue.[11] After his untimely death while testing on himself his hypothesis that chloroform and hydrocyanic acid could be a useful remedy for tinnitus in his patients,[12] his collection came into the possession of the Royal College of Surgeons, of which he had been one of the first members elected to fellowship.

ACADEMIC OTOLOGY AND OTOPATHOLOGY IN GERMANY

Tröltsch and His Colleagues. It was a visit to Toynbee in London and to William Wilde in Dublin that inspired the young Anton von Tröltsch (1829-1890) to give up the general practice of medicine upon his return to Würzburg and to become an ear surgeon.[5] His conversion marked the start of scientific otology as a clinical entity and an academic discipline. Subsequently Tröltsch was the revered senior member of the otologic professorial quadrumvirate that included Salom Moos (1831-1895) of Heidelberg, Adam Politzer (1835-1920) of Vienna, and Hermann Schwartze (1837-1910) of Halle. Together with younger academic colleagues like Friedrich Bezold (1842-1908) of Munich and his pupil Friedrich Siebenmann (1852-1928) of Basel, they set the pace for the remarkable and salutary advances made by clinical otology and otopathology in that era. Reports of those advances appeared regularly in the *Archiv für Ohrenheilkunde*, founded in 1864 by Tröltsch, Politzer, and Schwartze, and in the *Zeitschrift für Ohrenheilkunde*, founded in 1872 by Moos and Hermann Knapp of New York. The title page includes the words, "In deutscher und englischer Sprache." In fact, the *Zeitschrift* frequently published case reports from American otologists, but they were conscientiously translated into German by Moos or his associate Steinbrügge. After 50 years it was united with the *Archiv*, which continues in excellent health to this day, even though its name has twice been lengthened (in 1915 and 1966), then shortened (in 1973). Currently in its 246th volume, it flourishes as the *Archives of Oto-Rhino-Laryngology*.

Macroscopic Studies of Middle Ear Disease. The early continental reports of otopathologic studies, including that of Tröltsch[13] in 1859 on the temporal bones of 16 hard-of-hearing patients, were based on dissection alone, and attention was directed mainly to the condition of the tympanic membrane, ossicular chain, mastoid process, and eustachian tube. It was generally held that deafness was caused by pathologic changes in the middle ear. Lacking as yet a suitable method for examining the inner ear, Schwartze[14] and most other authorities considered "nerve" deafness to be a relatively rare phenomenon.

Caries and Necrosis. Among the favorite subjects of study were caries and necrosis of the temporal bone. In describing his method for postmortem examination, Tröltsch[15] had complained that only cases of that sort seemed to be of interest to pathologists. Even so, the first issue of the *Archiv für Ohrenheilkunde* welcomed a report by Toynbee,[16] also translated by Moos, of six such cases, which had resulted in extrusion of the remains of the cochlea or other portions of the diseased petrous bone. (Most of the patients seem somehow to have survived.) In the same volume Tröltsch called attention to a similar case that had been reported in the *American Medical Times*. The cochlear specimen recovered from that patient is illustrated in the American edition of Tröltsch's textbook,[9] translated by D. B. St. John Roosa (1838-1908) of New York.

Meniere. What was perhaps the most famous and influential temporal bone report in the otologic literature was likewise based on dissection alone. It was also one of the briefest: that by Prosper Meniere (1799-1862) describing, in his paper presented in 1861 to the French Imperial Academy of Medicine, the "red, plastic material, a sort of bloody exudate" that he once had found in the semicircular canals of a young woman at autopsy.[17] She was said to have died following exposure to extreme cold, having suffered what seems more likely to have been an attack of sudden deafness and vertigo than of Meniere's disease. In any case his argument was intended to show that a condition then generally referred to as "apoplectiform cerebral

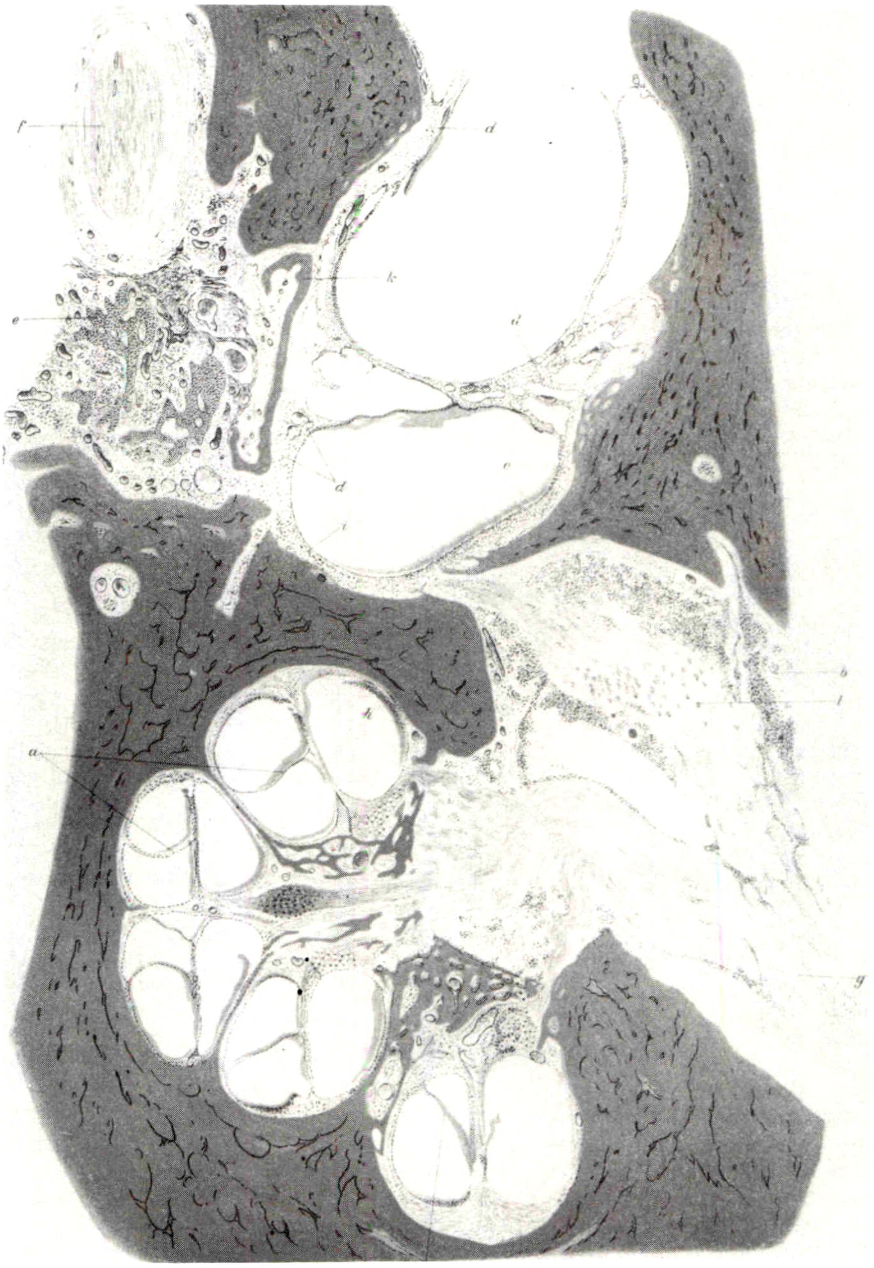

Fig 5. Cholesteatomatous invasion of vestibule and labyrinthine hydrops in 22-year-old patient with chronic purulent otitis media. (From Nager [1907].[33])

congestion," with vertigo, nausea, ataxia, hearing loss, and tinnitus, could have its origin in the labyrinth rather than in the brain and therefore did not require treatment by bleeding, as the medical wisdom of that day prescribed. Schwartze,[14] reviewing recent advances in otology, expressed some doubts about Meniere's interpretation, but hailed his contribution as most valuable for clinical understanding of the diseases of the inner ear.

Temporal Bone Sections. Although illustrations showing microscopic views of normal and abnormal tissues were already common enough elsewhere, it was not until 1884 that the first drawings of temporal bone sections appeared in the otologic literature. They accompanied an account by Moos and Steinbrügge[18] of their findings in the ears of two deaf-mutes. Only single turns of the cochleas were shown, one with a loss of spiral ganglion cells from Rosenthal's canal. In another, a small mass represented the remains of the organ of Corti, in which only supporting cells were to be seen.

By 1886 Moos[19] was able to publish the first lithograph of a midmodiolar section of the entire cochlea of a patient deaf after simple diphtheria uncomplicated by scarlet fever (Fig 1). In this early otobacteriologic study, he demonstrated a secondary invasion of the cochlea by a pathogenic microorganism, which he had identified as *Streptococcus*.

Nerve Deafness From Noise. Johann Habermann (1849-1935), then in Prague, was the first to demonstrate the effects of prolonged exposure to intense noise on cochlear structures.[20] In 1889 he described his findings in the inner ears of an elderly ex-boilermaker who had been run over by a train because he was too deaf to hear either its whistle or the warnings shouted by the crossing guard. Habermann described extensive areas in which Corti's organ was absent and cochlear nerve fibers had degenerated. Unfortunately, he included no illustrations.

Otosclerosis. The 19th-century histopathologic investigation of otosclerosis deserves a chapter to itself, if only because of the number of eminent otologists cooperating and competing, and the speculations and discussions generated by their varied findings. It has been summarized by Politzer in volume 2 of his *Geschichte*,[21] and has been presented in greater detail by Denker[22] in his monograph.

Among the numerous authors who described their histopathologic findings in otosclerosis, several deserve special mention. Katz[23] of Berlin was the first to report a study that included both functional tests during life and microscopic examination postmortem. He considered that the underlying problem was an arthritis of the stapediovestibular articulation, and recommended treatment with sodium salicylate. In 1894 Politzer[24] published a report of 16 cases of progressive otosclerotic deafness that he had presented the year before in Boston and Washington. He assigned the origin of the bony changes to the otic capsule, and not to the tympanic cavity, to which others had ascribed it. In one of his cases the process had invaded the scala tympani and had led to atrophy of cochlear nerve fibers. Four years later, Eduard Hartmann[25] (1871-1919), then in Siebenmann's clinic in Basel, published a description of otosclerotic involvement of almost the entire otic capsule (Fig 2). The organ of Corti appears not to have been affected.

From Siebenmann's later report[26] it became clearer that otosclerotic deafness not only was progressive, but might represent nerve deafness as well as conductive impairment. In his patient there was a significant reduction in hearing by bone conduction, accompanied by the formation of exostoses in the most basal portion of both scalae. Siebenmann insisted that the fundamental process was spongiotic in nature rather than sclerotic, and that it should be called *otospongiosis* rather than *otosclerosis*, as Politzer[24] had christened it. Even today this question of nomenclature has not been resolved fully, since valid arguments can be advanced in favor of either term, but the name otosclerosis seems to be as firmly established as it was 70 years ago.[21]

Infectious Diseases. Given the prevalence of middle ear disease and the lack of adequate medical treatment for such infections, there was great interest in the pathologic findings in otitis media and mastoiditis, as well as in labyrinthitis and cerebral abscess. Many other studies were concerned with deafness caused by infectious diseases, including mumps, syphilis, typhus, and tuberculosis. Although the studies often showed degeneration of Corti's organ and of cochlear nerve fibers, "nerve" deafness remained a somewhat shadowy and controversial entity. As early as 1893, however, Bezold[27] was able to distinguish clearly, by tuning fork tests and temporal bone sections, between the type of deafness caused by stapes ankylosis alone and that caused by typhus, with degeneration of nerve fibers in the osseous spiral lamina. Later studies by Paul Manasse[28,29] (1866-1927) of Strasbourg showed an example of the fibrotic mass that can form in the scala tympani of a luetic patient (Fig 3) and demonstrated hydrops in a patient who had been deafened by typhus (Fig 4).

Other Investigators. Among the other important contributors to knowledge of the histopathology of the inner ear in the years before and after World War I were Gustav Alexander (1873-1932) and Otto Mayer (1876-1951) of Vienna, Ernst Oppikofer (1874-1951) of Basel, Felix Nager (1877-1959) of Zürich, and Karl Wittmaack (1876-1972) of Jena and Hamburg. In the early 1900s Wittmaack made his studies of the histopathologic effects of noise and quinine on the ears of guinea pigs that marked the beginning of experimental otopathology.[8]

Further Progress. In 1889 Politzer[30] had described the method he used in preparing the temporal bone for histopathologic study. At the time of Hartmann's otosclerosis study[25] in 1898, serial sections had become commonplace. By 1917, when Manasse outlined the approved technique in his *Handbuch der pathologischen Anatomie des menschlichen Ohres*,[31] there had been a striking improvement, both in the technical quality of the inner ear sections produced and in the scientific and aesthetic value of the illustrations published. Among the many fine drawings appearing in the early 1900s, those in the articles by Alexander[32] on hereditary deafness and deaf-mutism and by Nager[33] on numerous types of hearing impairment (Fig 5) are particularly impressive for their wealth of cochlear detail. Around the turn of the century both colored lithographs, showing the staining properties of the various tissues, and some less informative photomicrographs were beginning to be used.

Significant progress in the histopathology of the inner ear continued to be made in the interval between World Wars I and II, especially in America and Britain, as well as on the Continent. Space does not permit reviewing either those or more recent investigations, which are doubtless already well known to students of the ear.

CONCLUSION

In spite of the important advances made throughout this century, there remains, as the late Stacy Guild firmly believed, much of interest and of value to be found in the publications of the older school of otopathologists. The extreme conditions they often depicted are now fortunately rare, but much of what they revealed, and perhaps even some of their misinterpretations, can still be relevant to present-day otologic problems. At the same time, the fact that batteries of reliable audiologic tests are now available for use in otologic diagnosis makes it all the more important to continue and to expand temporal bone histopathology by both classic and newer methods. Only in this way can closer correlations be established between clinical measurements of auditory and vestibular dysfunction and the type and extent of the underlying disorder, as bases for new insights and further improvement in the diagnosis and treatment of the diseases of the ear.

CURRENT STATUS OF THE OLDER TEMPORAL BONE COLLECTIONS

HAROLD F. SCHUKNECHT, MD

It was about 100 years ago that camera lucida drawings on the histopathologic changes of the temporal bone began to appear in otology publications such as the textbooks of Politzer. The techniques of these early days, while basical-

TABLE 1. HUMAN TEMPORAL BONE COLLECTIONS IN EUROPE

Locations	*Original Collectors*	*Current Custodians*	*Dates of Collections*	*No. of Bones*	*Clinical Records Available*
Würzburg	Manasse	Kley	1906-1943	850	No
Tübingen	Schwarz, Albrecht	Plester, Giebel	1923-1960	1,087	Dates, cause of death
Utrecht	Gerlings	Huizing, Veldman	1910-1972	92	Half of cases
Copenhagen	Kristensen	Bretlau, Jørgensen	1954-	757	Yes
Hamburg	Wittmaack	Rauchfuss	1906-1946	2,096	Yes
Leipzig	Lange	Oeken, Behrendt	1924-1945	1,500	Dates only
Zürich	Nager, Ruedi, Fisch	Fisch, Pollak	1909-	900	Yes
London	Hallpike	Williams, Davies	1930-1970	500	Half of cases

ly the same as those of today, were not sufficiently refined to provide information on the sensory and neural tissues, and their contributions to the field of pathology related mainly to connective tissues. For example, otosclerosis was identified as a disease entity of the bony labyrinth.

During the first half of the century, several large collections of serially sectioned human temporal bones were generated in Europe that served to document the pathologic changes of chronic infection, bone disease, and neoplasia. In 1985 I had the opportunity to examine eight of these older collections (Table 1).[34] In most collections the process of acquisition and preparation of the sets of temporal bones spans a period of several decades. In some instances it appears to have been a matter of prestige for a department of otolaryngology to possess a temporal bone collection, particularly a large one, and as a consequence emphasis was placed on numbers rather than quality. The amount of time and effort spent in developing a temporal bone collection is staggering. In most instances the collections are the product of a single person's effort; typically this person was an otologist and head of an academic department.

The historical documentation for these older collections is variable. Some of the medical records were lost during the bombing raids and fires in World War II. In none of these laboratories is there a systematic description of pathologic findings in association with a detailed narrative of the otologic history. Most of the older sets are not suitable for graphic reconstruction or for quantification of cochlear or vestibular disease because of missing sections, postmortem autolysis, and/or preparation artifact. The durability of the slides is quite impressive. The oldest set examined involved a case of otosclerosis and was prepared in 1906 (Wittmaack Collection). The mounting medium was clear, and staining quality (hematoxylin and eosin) was good. It seems probable that most sets will maintain their physical integrity for longer than 100 years.

Some collections are encumbered by sets of temporal bones having little or no scientific or teaching value for reasons of advanced postmortem autolysis, severe preparation artifact, absence of disease, or absence of medical records. Such sets need to be discarded or set aside to facilitate easier retrieval and study of the more valuable sets. Putting a collection into a more compact and orderly condition, as was done by S. K. Bosher for the Hallpike Collection, also minimizes the risk of its banishment in the event that space is needed for other departmental activities. When reorganized, it can provide much useful information on such subjects as bacterial infections, neoplastic diseases, congenital disorders, and trauma.

Among the currently active laboratories in Europe are those of Heinrich Spoendlin in Innsbruck, Ugo Fisch in Zürich, E. H. Huizing in Utrecht, Leslie Michaels in London, and Paul Bretlau in Copenhagen. At these laboratories newer methodologies, particularly electron microscopy, are being adapted in various ways to supplement serial sectioning for light microscopy.

TRAINING OF TEMPORAL BONE HISTOPATHOLOGISTS AND TECHNICIANS: PAST AND PRESENT

ROBERT I. KOHUT, MD

Supported in part by grants from the American Otological Society, Inc, Research Foundation and the National Institute on Deafness and Other Communication Disorders (R01 DC 00589).

Reviewing the history and development of medical thought and methods is more than rewarding. It is intriguing. Often, independent review can lead one to new conclusions that may in some instances augment the previous thoughts of others. Sometimes these conclusions contradict previous thoughts. Whichever the case, there are usually some new findings that allow understanding of the development and supported conjectures regarding the beginning. These would include circumstances that directed, even compelled, certain efforts by special people. Usually the findings support the statement by Riesco-McClure that "all progress is made in retrospect" (personal communication with S. Riesco-McClure, 1964).

The assignment of this topic to me by Dr Bluestone allowed me to indulge my curiosity — a luxury that we too seldom enjoy. It was also timely in that I was scheduled to be close to the origins of temporal bone histopathology in Germany. I had the opportunity for a firsthand vignette of the experience recently published by Schuknecht,[34] of visiting the institutions maintaining the original temporal bone collections. My opportunity was restricted after Uppsala and Lund to Leipzig (I could not go to Jena) and Chicago because of time and previous commitments. I believe, however, that my choices for the purposes of this presentation were, though incomplete, correct. Although I may have some new thoughts to share with you, I have, as is usually the case, developed more questions than answers. The charge to me was to see "how people were trained." An expansion to include "why they were trained" was inescapable. Let me share with you the sequence of events, the data I received, and some of the unanswered questions that developed regarding the chronology of the study of temporal bone histopathologic changes.

I had occasion to contact Dr George Nager (personal communication, 1988) regarding a paper by Ruttin (1921)[35] concerning perilymphatic fistulas and Ruttin's temporal bone studies. This was fortunate, in that Dr Nager was able to discuss with me and guide my thinking concerning the history of temporal bone histopathology. Several points developed during this conversation.

It seemed to both of us that Karl Wittmaack, as a professor of otolaryngology, was the main teaching source for the series of noted investigators who further developed and dominated the field in the early part of this century. The lineage included Wittmaack's teaching Friedrich Betzold, who in turn taught Friedrich Siebenmann, who taught Felix Nager, who in turn taught John R. Lindsay, who brought this study method to the western hemisphere. Dr Stacy Guild also studied with Felix Nager. We know that Drs Dorothy Wolfe, J. B. Walther, and Glen Weaver, among others, studied with Guild. Several here represent the many students of Lindsay, and from these Lindsay students there is a distinct cadre of students, some of whom are also here.

Introduction of temporal bone histopathology in Mexico was due to the efforts of Professor Bustamante Gurria, who wished to help develop a national institute of otolaryngology (personal communication with Raul Hinojosa, 1988). Professor Bustamante Balcoral, Gurria's son, was responsible for the supervision of the development of the temporal bone collection now in the National Institute of Cardiology in Mexico City. This was done at the same time that Dr Raul Hinojosa, a pathologist, was sent by Dr Bustamante Gurria to study with Lindsay at the University of Chicago in order to develop this activity in the institute. Unfortunately, the otolaryngology institute was never developed, and the collection did not expand.

We were also aware of Wittmaack's editorial efforts in the development of the *Henke Lubarch Handbook of Special Pathology*, volume 12. Contributors included E. Mobius, M. Coch, Wilhelm Lange, H. Marx, H. G. Runge, and Otto Steurer. Where did they learn? How did they execute their studies? I have not been able to devote the time to answer these questions except in part. Two points of information: first, some may have been students of or assistants to Wittmaack; second, Lange deserves special attention. I will in a moment address the relationship of Lange and Wittmaack to the origin and development of temporal bone histopathology.

I had the opportunity in June of this year, during the 15th Barany Society Meeting in Uppsala, prior to going to Germany, to speak to Professors Alf Meyer, Jan Stahle, Toru Matsunaga, Takuya Uremura, Hiroshi Sasaki, and Hans Engstrom regarding this history of training and preparation. Engstrom informed me that Professor Otto Meyer of Germany had made improvements in processing techniques (personal communication, 1988). Stahle[36] mentioned in his remarks concerning hydrops that Kyoshiro Yamakawa had, just before Cairns and Hallpike, reported the histopathologic findings in Meniere's syndrome. Matsunaga is still in communication with T. Hasagawa, a student and colleague of Wittmaack's, now an octogenarian, and promised some material and photographs. Uremura and Sasaki discussed the history and development in Japan of this discipline, including the names Yasuya Nomura, Junichi Suzuki, Tetsuo Ishii, and Tonijoma. Meyer indicated that Professor Zangemeister, a member of the Barany Society, is the son of the Professor Zangemeister who was Wittmaack's last co-worker. It seemed from all sources that the early temporal bone histopathologists did their own specimen processing. As yet, I have not found out when this task passed from histopathologist to histopathology technician.

Professor Ursula Winkler of The Karl Marx University, Leipzig, was extremely helpful in guiding me in the institution, showing me the temporal bone collection, and translating from the history of the department, as well as from the writings of Lange, Wittmaack, and others.

It became apparent that Professor Lange and Professor Wittmaack were both active as temporal bone histopathologists at the same time. They never worked together at the same institution. Both prepared their own specimens, according to Professor Winkler regarding Lange, and Professor Schuknecht regarding Wittmaack.[34] The question arises, where did they learn? Who or what was the inspiring element common to both? Was there any relationship to Professor Paul Manasse (1866-1927), who started his temporal bone slide collection in Strasbourg, fully developing it as chairman of the department of otolaryngology in Würzburg?

WHO TAUGHT WITTMAACK AND LANGE?

It seems that there is one point of education that Wittmaack and Lange had in common, which is related to Leipzig. This is suggested if one follows the chronology of these peers relating them to E. P. Freidrich, assistant to Professor Barths, Leipzig. It seems, therefore, that Professor E. P. Freidrich was the common element in the developing academic pursuits of both Lange and Wittmaack. His major interest in temporal bone surgery and the anatomy of purulent labyrinthitis may have served as the nidus of inspiration for his student Lange until 1899 and his assistant Wittmaack after 1899. I have not yet reviewed Freidrich's work, so I can comment on neither his activities concerning temporal bone histopathology nor any possible link with Manasse. The activities and interests of Wittmaack and Lange remain, however, inextricably associated with Professor E. P. Freidrich.

Somewhere, at some time, the duties and talents for celloidin embedding and temporal bone preparation passed from the histopathologist to the temporal bone histopathology technician. Tracing backward, we know that Lindsay did not do such preparations. Did his teacher Nager? If not Nager, did Siebenmann? The story of the transition is probably very interesting.

It is obvious that a professor trained the first technician. Was this the subsequent pattern of teaching? Probably not, as evidenced by that related to me by the most senior (and expert) technician of my acquaintance. Ayako Hammamoto, as a Japanese scholar in literature, states that she joined Dr Lindsay at the University of Chicago because jobs for literature scholars were unavailable (personal communication, 1988). Hers was not tutorial training. She was given an outline of directions for specimen preparation, guinea pig temporal bones, and elbow positioning instructions from Robert Kimura. When she was questioning Lindsay about specimen orientation for sectioning, he once suggested x-ray evaluation. This, she said, was no help. When asked, "Well, then who taught you?" she answered, "I taught myself."

Today, for temporal bone technician training, more typically a person familiar with paraffin embedding methods is sent to established laboratories to learn celloidin techniques. We recently sent Phillip Heitmann to Dr Schuknecht's laboratory in Boston, then on to Dr David Lim's laboratory in Ohio. This process appears very successful for this high level of training.

Currently, a temporal bone histopathologist's training usually starts in the otolaryngology residency with regular reviews of histopathologic anatomy and pathology. This is inadequate for serious studies. These studies require tutored specimen evaluations, some of which include cochlear reconstruction and quantitative evaluation. Continued study of prepared specimens coinvestigated with more senior, experienced temporal bone histopathologists allows the developing temporal bone histopathologist to mature to independent activities. Only a few with training in general pathology have had experience in this area. These include Ruth Gussen, Ivan Holleman, and Raul Hinojosa. This lack of training in general pathology of most temporal bone histopathologists may be the reason that most reports of temporal bone histopathologic findings are associative and do not emphasize histopathologic mechanisms and pathogenesis. The danger in association of a pathologic change with an element of the medical history of the patient is that conjecture cannot be avoided. Expanding our training to include predictive studies wherein the pathologic change is predicted by the history and vice versa may lead to the development of an expanded fund of knowledge regarding pathologic mechanisms and pathogenesis of otologic disorders.

Last, a new era of histologic evaluations of the membranous labyrinth has developed during the lifetimes of all who are present at this meeting. The story of labyrinthine electron microscopy is interesting and underscores Riesco-McClure's statement, "All progress is made in retrospect." Unique coincidences and circumstances usually mold these progressive activities; so it was with Professor Hans Engstrom. It so happened that Engstrom was working in the histology department at a time that the professor of histology was to go on sabbatical leave. For special reasons, Engstrom was made department head in the professor's absence. At the same time Engstrom had clinical responsibilities in otolaryngology. Through this set of circumstances, while he was working, as he strongly states, with Jan Wersall, pieces of membranous labyrinth were acquired at surgery during destructive procedures. Fixed in osmic acid, these specimens were evaluated with the electron microscope. Making surface preparations by the technique of drilling away the labyrinth capsule was a natural outcome of the special surgical talents of Engstrom and the special histologic talents of Wersall (Hans Engstrom, personal communication, 1988). Many have been trained by these men and their students, some of whom are here today.

We are sure, however, of the development of electron microscopic techniques and training by Engstrom and Wersall Although less than a century old, the origin of techniques and training methods for temporal bone light microscopy remains elusive, but is related to the names Manasse, Freidrich, Wittmaack, and Lange.

DISCUSSION

The Workshop conferees recognized the invaluable contribution of those scientists who devoted their careers to collecting and studying human temporal bones and advancing our scientific knowledge. They also recognized that those who initiated temporal bone collections in Europe and the United States taught their students by role modeling, and their students went on to teach the present generation of temporal bone pathologists. In addition, it became evident from the reports that several temporal bone collections in Europe and the United States are now in disuse and may be lost forever either by neglect or even by being discarded. The workshop conferees concluded that a review of the history of temporal bone pathology makes clear to us that future trainees can be taught most effectively by those clinician-scientists who are actively engaged in human temporal bone research. In addition, the workshop conferees strongly urged that a central repository be established to receive temporal bone collections along with historical information from institutions that are no longer involved in human temporal bone research, so that these invaluable collections will not be lost to current and future generations of investigators. Alternatively, an orderly system of transfer of this material to active laboratories could be facilitated.

CONTEMPORARY STATE OF THE ART AND KNOWLEDGE

EUROPEAN FUNCTIONAL HISTOPATHOLOGY PROGRAM

GREGORY R. BOCK, PHD, DSC

INTRODUCTION

The European Economic Community (EEC) is a group of 12 European countries. The central administrative apparatus of the EEC is located in Brussels, and although the activities of the EEC administration are oriented primarily toward commercial matters, there is also a scientific program. Included in the scientific program is a section dealing with medical research, which is able to fund joint European activities in the fields of medicine and public health.

The guiding principle of the EEC medical research program is that money provided by the program should be used for coordinating research rather than for funding research directly. Each member country of the EEC has a complex system of research councils and other funding agencies that provide money to fund research. Since the Commission of the EEC is a supranational structure, it is considered more appropriate for its funds to be used to coordinate the various national research efforts in different fields of biomedical research.

The medical research program of the EEC has, since 1974, included a specific section dealing with research on hearing impairment. From 1980, this has included a program on functional histopathology of the human audiovestibular organ, directed by Salvatore Iurato. The purpose of this paper is to give a brief description of the main activities of this functional histopathology program. Three major areas of activity have developed since 1980. First, a European temporal bone bank scheme has been initiated; second, a series of meetings has been held on human temporal bone histopathology; third, working groups have been set up to deal with specific problems.

TEMPORAL BONE BANK SCHEME

Strictly speaking, this is not a temporal bone bank, but a centralized data base for coordinating the information collected in different European laboratories. It was decided that human temporal bone histopathology, particularly in relation to audiometric and neurophysiologic data, would be greatly facilitated if European investigators could interrogate a central data base to obtain information on the availability of processed temporal bones from patients on whom various hearing tests had been carried out. It also was decided that it would be unrealistic to attempt to store the results of such tests in the data base. Consequently, the data base contains information on how and where a given temporal bone was processed and stored, and which hearing tests, if any, were carried out before the patient died.

An important aspect of the scheme is the agreement of the major European histopathology laboratories to receive and process temporal bones sent by investigators who lack the facilities to carry out such processing. These major laboratories have become participating institutions in a network of processing laboratories that should, in principle, make it possible for any European investigator to study a temporal bone, provided that the investigator can perfuse and remove the bone.

Two meetings were held in 1981 to prepare a manual[37] describing the preferred procedures for perfusing and removing human temporal bones. The manual contains a checklist that can be photocopied and sent to the data bank, giving comprehensive information about the patient. A separate checklist is completed by the receiving laboratory, giving information on how the temporal bone was processed.

The European temporal bone bank scheme was launched in 1983 with the publication of two papers[38,39] describing the program and announcing the availability of the manual. At the time of writing (July 1988) the data base contains data on approximately 100 temporal bones. There have been many requests for the processing manual, and a revised version is now in preparation.

WORKSHOPS

The second major activity organized under this program has been a series of workshops on human temporal bone histopathology. These workshops have been closed (ie, attendance by invitation only) meetings organized by a small committee (S. Iurato, G. Bredberg, G. Bock). Meetings have been held in Brussels (in 1983) and in Milan (in 1984 and 1986). The first meeting concentrated mainly on techniques for processing temporal bones. Data from many studies of human temporal bone histopathology were presented at the two Milan meetings, and the proceedings of both meetings were published.[40,41] A further meeting is planned for 1989.

WORKING GROUPS

In 1984, S. Iurato convened a small working group to study the feasibility of combining data from different laboratories to produce a comprehensive description of the hair cell distributions in the "normal" human cochlea. The irregular pattern of human cochlear hair cells makes it difficult to count missing cells, and it is therefore difficult to assess the "normality" of the hair cell populations of a given temporal bone. This group continued to meet regularly and concluded that data could be provided by three different investigators (A. Wright, G. Bredberg, L. Ulehlova). Most of the adult temporal bones in this study came from patients whose hearing was known to be normal for their age.

The group produced a report[42] giving comprehensive statistical analyses of the hair cell distributions plotted in a number of different ways. In spite of the inevitably uneven age distribution of the temporal bones in this study, the data provide a useful standard against which other investigators can compare individual cases to see if they are within the normal range for a given age.

The group which produced the report on hair cell distributions is now meeting to consider the feasibility of a similar study of ganglion cell distributions.

CONCLUSION

The European functional histopathology program has provided a timely and effective stimulus to European studies of the human temporal bone. Many lasting collaborations have developed as a result of our regular workshops, and it is to be hoped that this program will provide continuing encouragement and support for European studies in this difficult but important field.

HUMAN TEMPORAL BONE STUDIES IN JAPAN

YASUYA NOMURA, MD

In Japan the largest medical society related to otolaryngology is the Oto-Rhino-Laryngological Society of Japan, Inc, founded in 1893. Members of the Society have developed 14 medical societies limited to specific fields of otorhinolaryngology. Four of these 14 are concerned with otology: the Japan Society of Ear Research, the Japan Society for Equilibrium Research, the Japan Society of Clinical Otology, and the Japan Audiological Society.

As evidence of the status of human temporal bone research in Japan, we have investigated the numbers and categories of papers presented at the annual meetings of these societies for the past 10 years. Human temporal bone studies can be classified into five categories: 1) temporal bone histopathology using serially sectioned celloidin specimens, 2) studies of embryos using paraffin specimens, 3) studies using transmission electron microscopes or scanning electron microscopes, 4) studies using surface preparation techniques, and 5) others.

Presentations during the period 1978 through 1987 are classified and listed in Table 2, which shows that 24 papers were presented at the meetings of five societies in 1987. The total number of papers on all subjects was 1,160. Nineteen of the 24 papers presented reported on histopathology of celloidin human temporal bone specimens.

CELLOIDIN SPECIMEN STUDIES

During the period 1978 through 1987, a total of 8,922 papers were read at meetings of these societies, of which 207 (2.3%) concerned the human temporal bone, and 130 of these 207 (62.8%) were celloidin human temporal bone studies. As befits its name, the Japan Society of Ear Research contributed a great deal. The number of presentations to individual societies were as follows: Japan Society of Ear Research, 67; Japan Society of Clinical Otology, 34; Japan Audiological Society, 11; Oto-Rhino-Laryngological Society of Japan, Inc, ten; and Japan Society for Equilibrium Research, six.

Of the 130 papers dealing with celloidin specimens, 80 were case reports and 50 were basic studies. The topics of these papers are listed in Tables 3 and 4. These studies were conducted in 23 universities and three hospitals. Ninety percent of the investigators were former students of Dr Schuknecht or were studying under Dr Schuknecht's former students.

PARAFFIN SPECIMEN STUDIES

Research studies on embryos using the paraffin technique were far fewer during the period 1978 through 1987 compared to celloidin specimen studies. The titles of the papers in this category concerned development of the otic vesicle, round window, facial nerve, sinus tympani, attic, eustachian tube, middle ear, and antrum.

TRANSMISSION AND SCANNING ELECTRON MICROSCOPY STUDIES

These represented 23% of the human temporal bone studies carried out from 1978 to 1987. The titles show that the subjects of those studies were the stapediovestibular joint, the surface of the middle ear mucosa, the stapedius and tensor tympani muscle, the round window membrane, the organ of Corti, stereocilia, degeneration of stereocilia of the external hair cells, giant hairs, the basal body of cochlear sensory cells, the tectorial membrane, the imprint on the tectorial membrane, nonsensory ciliated cells, nerve fibers in the organ of Corti, development of

TABLE 2. BREAKDOWN OF PRESENTATIONS OF RESEARCH ON TEMPORAL BONE AT MEETINGS OF FIVE JAPANESE ACADEMIC SOCIETIES

	Celloidin	*Paraffin Embryo*	*TEM-SEM*	*Surface*	*Others*	*Total*	*No. of Presentations in All ENT Fields*
1978	8		6		2	16	727
1979	8	1	5		1	15	609
1980	9		5	1	2	17	747
1981	15	3	3	1		22	798
1982	12	1	9		3	25	864
1983	13		5		1	19	888
1984	15	1	6		3	25	985
1985	16	3	2		2	23	984
1986	15	1	4		1	21	1,160
1987	19	1	2		2	24	1,160
Total	130	11	47	2	17	207	8,922

TEM — transmission electron microscopy, SEM — scanning electron microscopy.

TABLE 3. THEMES OF CASE REPORTS

Acute bilateral deafness and nephritis
Adhesion of tympanic membrane
Apical hydrops
Atresia auris congenita with chromosome abnormalities
Bacterial labyrinthitis
Behçet's disease
Cancer of middle ear
CHARGE association
Cholesteatoma
Cloverleaf skull syndrome
Complete loss of organ of Corti
Congenital anomaly of inner ear
Congenital anomaly of oval window
Congenital spondylo-epiphyseal dysplasia
Cryoglobulinemia
Cyclopia
DiGeorge's syndrome
Disseminated candidiasis
Down syndrome
Drowning
Eardrum of Kawasaki's disease
Endolymphatic collapse
Facial nerve defect
Fanconi's anemia
Fluctuating hearing loss
Goldenhar's syndrome
Head injury
Hearing loss and renal dialysis
Hearing loss due to cisplatin administration
Hunter's syndrome
Invasion by maxillary or nasopharyngeal cancer, or by parotid gland tumor
Klippel-Feil syndrome
Leukemia
Malignant lymphoma
Malignant otitis externa
Meniere's disease
Mondini dysplasia, histopathology and computed tomography
Monostotic fibrous dysplasia
Multiple endocrine neoplasia type 2B associated with marfanoid habitus
Osteogenesis imperfecta
Otitis media mucosa, squamous epithelium junction
Otosclerosis and endolymphatic hydrops
Presbycusis
Primary squamous cell carcinoma of the ear
Positional vertigo
Profound noise-induced deafness
Scheibe dysplasia
Serous otitis media
Serous otitis media, immune insufficiency
6p partial monosomy
Squeeze
Subarachnoid hemorrhage
Temporal bone metastasis of maxillary cancer, lung cancer, gastric cancer, and thyroid cancer
Thanatophoric dwarfism
Total ossicular replacement prosthesis in stapes surgery
Trisomy 18
Tympanosclerosis
VATER syndrome
Vestibular pathologic findings in labyrinthine hemorrhage
Wegener's granulomatosis
Wilson's disease

TABLE 4. THEMES OF BASIC STUDIES

Anatomy of epitympanum
Blood flow of fallopian canal
Branch of singular nerve in otic capsule
Celloidin method versus scanning electron microscopy
Chronic inflammatory process in middle ear
Chronic otitis media
Classification of inner ear anomalies
Congenital anomalies and endolymphatic hydrops
Congenital anomaly of oval window and facial nerve
Content of endolymphatic sac
Crista neglecta
Cupula
Dehiscence of fallopian canal
Distribution of ganglia in tympanic plexus
Distribution of melanin
Distribution pattern of blood in facial nerve following subarachnoid hemorrhage
Endolymphatic hydrops and disease of vestibular aqueduct and endolymphatic sac
Endolymphatic sac pathology
Facial nerve with tumor invasion
Fenestration operation
Fetuses, maternal rubella
Graphic reconstruction
Graphic reconstruction of vestibular aqueduct
Irradiation to head and neck cancer
Lenticular process of incus
Measurement of stapes
Measurement of stria vascularis
Measurement of vestibular aqueduct and endolymphatic sac
Microfissure in oval window area
Otitis media and endolymphatic hydrops
Otitis media in infants with cleft palate
Sclerosis of perisaccular tissue
Serial vertical sectioning
Spatial occupancy ratio of arteries in and outside facial nerve
Spiral ganglion aging
Stapes surgery and fenestration
Three-dimensional reconstruction of temporal bone
Vascularity of endolymphatic sac
Vestibular aqueduct and paravestibular canaliculus in inner ear anomalies
Visualization of human vestibular aqueduct with computer-aided serial section reconstruction system

stereocilia in the fetus, Reissner's membrane, melanocytes in the inner ear, cochlear vasculature, vestibular vasculature, the otolithic membrane, nerve endings in vestibular sensory cells, multipolar neurons in the vestibular ganglia, dissection using micromanipulators, the endolymphatic sac of a patient with Meniere's disease, monostotic fibrous dysplasia, cochlear changes after cisplatin treatment, sudden deafness, facial nerves, congenital anomalies, virus-like particles in vestibular ganglion cells, glia cells in the vestibular nerve, and vasculature in the human mastoid.

SURFACE PREPARATION STUDIES

Surface preparation techniques were used to investigate Reissner's membrane and its vasculature.

OTHERS

The following structures or themes were studied by use of techniques other than those previously mentioned: the tympanic mucosal fold, the tympanic isthmus, the round window membrane, the stapes, the stapedial nerve, morphology of the intratemporal facial nerve, thick temporal bone specimens, type II collagen in the middle and inner ear, and Feulgen-DNA cytofluorometry on the component cells of the cochlea.

HARVESTING TEMPORAL BONES: THE CLINICIAN'S CONTRIBUTION

HORST R. KONRAD, MD

Collecting useful temporal bone material is an exacting and complex process. To be of value in studying normal function and temporal bone disease, meticulously collected clinical information about the patient's life must be correlated with quickly and carefully collected and processed temporal bones. As soon as energy processes cease after death, autolysis occurs and the postmortem changes quickly destroy the value of the collected specimens. This is particularly true if we plan to look at fine structure or molecular processes. Central nervous system tissue also quickly deteriorates, and small processes and terminals especially are obliterated quickly. Chemical mediators probably last only seconds to minutes. Time is of the essence, as many of these postmortem changes take place during the first few minutes after death. In order to avoid delays, the clinician must make contact with the patient and the family prior to death. In the present day of organ donation, it is not unexpected that patients and their family members may be approached by the clinician prior to the patient's death with a request for permission to obtain temporal bones and brain tissue. This can be facilitated further if the clinician lays the groundwork for this request at the time the patient is recruited into the temporal bone bank program.

Ideally, temporal bones should be collected by the methods described by Schuknecht,[43] since this allows the removal of the entire brain and the temporal bones. Even if the patient or the family is reluctant to agree to a formal autopsy, a request for an organ for study or a limited autopsy might be honored by the patient and family members. This is particularly critical with the declining rate of autopsies since the Joint Commission on Accreditation of Hospitals stopped reviewing autopsy rates as part of the hospital accreditation process. A method similar to the one described by Nadol[44] or the method used by the University of Virginia[45] then can be used to remove the temporal bones. By removing a second bone flap from the squama of the temporal bone, one can now remove a sample of temporal, parietal, and frontal cortex, a sample of cerebellum, and the brain stem.

In order to obtain particularly well-fixed temporal bones, the clinician can discuss immediate postmortem perfusion of the temporal bones with the patient and family. If permission is granted, communication has to be established among the nursing staff, the attending physician, and the otolaryngology house staff. Of course, the house staff has to be trained in perfusion techniques and know where the perfusion materials and an operating microscope are kept. Even more important, they must have a personal interest and a "stake" in the proper perfusion and removal of temporal bones. This is accomplished easily by including the house staff in the subsequent write-up and publication of articles resulting from studies of the temporal bone materials.

As soon as the patient is pronounced dead, an orderly process of communication needs to go into effect. The resident or faculty member is called, the cadaver is perfused,[42] and the tissue is collected as soon as the cadaver can be moved to the morgue. Immediate cause of death and the state of the patient just prior to death should be recorded also, since this information may have a bearing on the collected materials.

HARVESTING TEMPORAL BONES: THE UNITED STATES EXPERIENCE

HAROLD F. SCHUKNECHT, MD

Prior to World War II, the two temporal bone collections of substance were located at The Johns Hopkins University under the direction of Stacy Guild and at the University of Chicago under John Lindsay.

In 1955 the Subcommittee for Research of the Committee for the Conservation of Hearing of the American Academy of Ophthalmology and Otolaryngology (AAOO) became actively engaged in stimulating research in otology. During the next several years, the Committee sponsored several exhibits on human temporal bone pathology at the annual meetings of the AAOO. In 1960, the Committee for the Conservation of Hearing was phased out, and the AAOO created a Committee for Research. In addition to exhibits, the Committee established annual research meetings and awards for research. The importance of human temporal bone pathology was constantly stressed, and several new temporal bone laboratories were created within departments of otolaryngology for purposes of research and teaching. These laboratories were supported in part or wholly by research grants from federal and private agencies, but principally by the National Institutes of Health (NIH).

Further impetus to otologic research derived from the formation of the Deafness Research Foundation (DRF) in 1958. In its role as a granting agency, it has supported many human temporal bone studies during the ensuing years. The research fund of the American Otological Society, Inc, also has supported human temporal bone

TABLE 5. HUMAN TEMPORAL BONE COLLECTIONS IN UNITED STATES

<100 Bones	*100 to 300 Bones*	*300 to 1,000 Bones*	*>1,000 Bones*
University of Florida, College of Medicine, Gainesville	Henry Ford Hospital, Detroit	House Ear Institute, Los Angeles	The Johns Hopkins Medical Center, Baltimore
Medical University of South Carolina, Charleston	Ear Research Foundation of Florida, Sarasota	University of Michigan, Ann Arbor	University of Chicago
Memphis Eye and Ear Hospital	University of Pennsylvania, Philadelphia	New York University, New York	University of Minnesota, Minneapolis
University of Virginia Medical Center, Charlottesville	Tufts Medical School, Boston	Baylor College of Medicine, Houston	Massachusetts Eye and Ear Infirmary, Boston
University of Texas Health Science Center, Dallas	Mayo Graduate School of Medicine, Rochester, Minn	University of California, Los Angeles	The University of Iowa, Iowa City (includes Barry J. Anson embryology collection of 700)
Northwestern University, Chicago	New York Hospital, New York	Columbia University, New York	
University of Illinois, Chicago	Upstate Medical Center, Syracuse	Pittsburgh Eye and Ear Hospital	
William Beaumont Hospital, Royal Oak, Michigan		University of Wisconsin, Madison	
University of Oklahoma Health Science Center, Oklahoma City		Ohio State University, Columbus	
Washington University Medical School, St Louis			
Mercy Hospital, Chicago			
Hershey Medical Center, Hershey, Pa			
Bowman-Gray School of Medicine, Winston-Salem, North Carolina			
Albert Einstein College of Medicine, New York			

studies, but it is mandated to restrict its support of research to the amelioration of hearing loss caused by otosclerosis.

In 1960, the directors of the DRF encouraged the founding of a National Temporal Bone Bank (TBB) program, which was strongly supported by the Committee on Research of the AAOO. The principal objective of this program was to identify prospective temporal bone donors with ear disease and to acquire their pledges. Regional centers were established at The Johns Hopkins University, the University of Chicago, Baylor College of Medicine, and the University of California at San Francisco. The program was supported initially by grants from the DRF and later by NIH (1968-1971). In 1971, the grants award committee of the DRF recommended that the regional centers be consolidated into a single national center for reasons of efficiency and economy. The National Temporal Bone Bank Center (NTBBC), therefore, began its work in 1972 at 550 N Broadway, Baltimore, under the direction of John Bordley and later George Nager of The Johns Hopkins University School of Medicine.

While it appeared that economy could be served by the NTBBC, it became obvious that a national center was not a suitable mechanism for acquiring pledges on a national scale. For example, 5,600 pledges had been acquired in the 11 years prior to the establishment of the national center, but only 480 were added during the subsequent 6 years.

The DRF then appointed an advisory committee to make recommendations concerning the future of the TBB program. This committee recommended that the program again be decentralized into four regional centers. The locations of the regional centers and their directors and associate directors are as follows:

1. Eastern TBB Center, Massachusetts Eye and Ear Infirmary, Boston. Director, Harold Schuknecht; Associate Director, Joseph Nadol.
2. Southern TBB Center, Baylor College of Medicine, Houston. Director, Bobby Alford; Associate Director, Makoto Igarashi.
3. Western TBB Center, UCLA Medical Center, Los Angeles. Director, Paul Ward; Associate Director, Ruth Gussen.
4. Midwestern TBB Center, University of Minnesota, Minneapolis. Director, Michael Paparella; Associate Director, Marcos Goycoolea.

The total number of pledges and medical records in the four regional centers is now 6,655. About 50 pairs of temporal bones are acquired each year from persons who pledged their temporal bones for research through the temporal bone bank program.

Although the scientific purpose of both the temporal bone bank and the temporal bone laboratories is to acquire new knowledge on the pathologic basis for auditory and vestibular disease, their modes of action are quite different. The temporal bone banks' purpose is to acquire donors, to act as repositories for medical records of those donors, and to provide information and assistance in the removal of temporal bones. The temporal bone laboratories, on the other hand, accept and prepare the temporal bones and provide for their study and interpretation. The temporal bone banks are supported by grants from NIH, DRF, and institutional funds at the four centers, while temporal bone laboratories are supported entirely separately, usually in the form of grants to otopathologists. The removal and preparation of human temporal bones are outside the province of hospital pathology departments because of the expense, time, and effort required, and because of the special interest and knowledge needed to interpret the preparations. The study of human temporal bone disease, therefore, becomes a research endeavor and must be supported by departmental funds, grant monies, or both. Table 5 presents a list of temporal bone laboratories in the United States and the approximate number of histologically prepared temporal bones in each collection.

I should not fail to mention that there are several small but growing temporal bone collections in Japan. Few otologists are aware of the fact that Yamakawa[46] of Japan independently discovered endolymphatic hydrops in Meniere's disease and reported his findings in 1938, yet in the western world we give the credit for this discovery to Hallpike and Cairns,[47] whose report was published later that year. Another fine collection is being groomed at the University of Toronto under the direction of Peter Alberti and Michael Hawke.

DISCUSSION

The Workshop conferees asked Dr Schuknecht approximately what percent of contributions listed in his report could be directly attributed to the National Temporal Bone Bank Program. His answer was approximately 20%.

HARVESTING BRAINS

RAUL HINOJOSA, MD

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Correlative studies of central auditory and vestibular systems and peripheral auditory and vestibular organs are rare. Brain is removed routinely at complete autopsies. However, there is not a routine or systematic removal of portions of the central auditory and vestibular systems or other sense organs for pathologic studies.

BRAIN REMOVAL

The brain is removed by the classic method, which consists of cutting the scalp by following an imaginary coronal plane connecting the mastoid of one side to the mastoid of the opposite side. After the two halves are reflected forward and backward, the skull is opened with a Stryker autopsy saw with a round cutting edge blade by any of the different methods (circular, wedge, triple notch) designed to avoid slippage of the skull at the time of embalming. Ideally, sawing should be stopped just short of cutting through the inner table of the cranium to avoid cutting through the meninges and the brain. To detach the brain, the frontal lobes are raised gently and the cranial nerves are cut in numerical order as close to the base of the skull as possible. The pituitary stalk and the arteries and veins are cut as well. The tentorium is cut with scissors, and finally the spinal cord. The brain is weighed and fixed.[48]

FIXATION

The routine fixation technique used in the autopsy room is by immersion in 10% buffered formalin for 10 to 14 days. The brain is suspended upside down in the fixative by means of a thread passed underneath the basilar artery at the level of the pons to prevent distortion.

PERFUSION

Perfusion of the fixative has the advantage of faster and complete fixation, especially in deeper portions of the brain, improving the fixation quality and fixation time. Fixation of the brain in situ or after removal can be accomplished by introducing a cannula into the carotid or vertebral arteries and injecting, first, isotonic saline solution, followed by 10% formalin solution; after immersion in the same fixative, satisfactory fixation for dissection can be obtained in 7 to 10 days.[48]

Even though the best routine fixative that allows the widest choice of stains for the nervous tissue is 10% formalin, there are other fixative solutions that give better results for specific staining techniques. The following fixatives give good results after being introduced by perfusion.[49] A general fixative for both light and electron microscopy of brain tissue is a mixture of 4% phosphate-buffered paraformaldehyde and 1% glutaraldehyde solution. This fixative gives good preservation of cellular structures; however, it interferes with immunologic studies.

The fixative for immunologic studies is a solution of 4% paraformaldehyde in phosphate buffer. The specimens obtained can be examined by both light and electron microscopy techniques.

There is no universally satisfactory fixative for immunohistochemistry, but Carnoy's solution (containing absolute alcohol, chloroform, and glacial acetic acid) preserves more antigens than formalin.

For enzyme histochemistry of horseradish peroxidase (for neural connections) the fixative to use is a combination of 1.25% glutaraldehyde with 1% paraformaldehyde or a 1.5% to 2.5% glutaraldehyde solution alone.

Another fixative used for special stains is Bouin's fixative, which is a mixture of picric acid, formaldehyde, and glacial acetic acid. This fixative preserves certain neuropeptides.[50]

DISSECTION OF BRAIN

After external examination for gross lesions such as hemorrhage, infarcts, thrombosis, aneurysms, etc, the brain stem and cerebellum, as a block, should be separated from the cerebral hemisphere. It is essential to section through the midbrain along a flat surface perpendicular to the neuraxis. For this purpose, with the brain placed upside down the scalpel is held in a pen-holding position with the tip of the blade in front of the cerebral peduncle a few millimeters above the tip of the mamillary body. After stabbing into the midbrain, the blade is brought toward the prosector. It is then flipped over and moved forward along the same plane. A gentle pull with the left hand on the brain stem and cerebellum during the procedure helps to complete the sectioning.[48]

SELECTION OF TISSUE BLOCKS FOR HISTOLOGIC EXAMINATION

Four different areas are selected for the study of the central auditory system: 1) the cochlear nuclei including the eighth nerve, 2) the inferior colliculi, 3) the medial geniculate body, and 4) the auditory cortex.

The block containing the cochlear nuclei is approximately 10 mm in thickness, centered at the pontomedullary junction. This block also includes the eighth nerve. The dorsal cochlear nucleus curves over the dorsolateral surface of the inferior cerebellar peduncle, extending into the floor of the lateral recess of the fourth ventricle. The ventral cochlear nucleus lies beneath superficial pontine tissue. The cochlear nerve extends into the cerebellopontine angle.

In order to include the inferior colliculi completely, the recommended thickness of the block is 10 mm. The inferior colliculi form the caudal half of the mesencephalic tectal plate. Each inferior colliculus is irregularly rounded, with a diameter of 6 to 7 mm, and consists of a dorsal superficial cortex, a central nucleus, and a pericollicular tegmentum.

The medial geniculate body, reached through the brachium of the inferior colliculus, appears at the surface as a small rounded elevation on the posterior aspect of each thalamus. The block for the medial geniculate nucleus should include the superior brachium in order to contain the complete nucleus. This block is also 10 mm in thickness.

The block for the auditory cortex is also 10 mm in thickness and should contain the superior temporal gyrus at the posterior end of the sylvian fissure. The vestibular nuclei complex extends from the superior cerebellar peduncle rostrally to below the level of the emergence of the facial nerve root caudally.

EMBEDDING

After appropriate time in the fixative, which varies from one technique to another, the tissue is dehydrated and embedded in either paraffin or celloidin. Frozen sections are used for silver stains and for special immunologic studies, because dehydration is not needed. Celloidin embedding produces less distortion, and larger blocks can be used than with paraffin embedding. For electron microscopy the tissue is embedded in epoxy resin.

STAINING

A variety of staining techniques are available for the morphologic analysis of the nervous system. These techniques include hematoxylin and eosin for general staining, Klüver and Barrera stain for nerve cells and myelinated fibers, Nissl stain for nerve cells, iron-hematoxylin for myelinated fibers, a number of silver stains such as Golgi and Golgi-Cox for selective neural staining, Cajal and Bielschowsky stain (neurofibrillar methods) for the study of degenerating axons, Nauta and Fink-Heimer stain for degenerating axons and nerve terminals, Bodian stain for nerve fibers and nerve endings, Glees stain for degenerating axoplasm, and Nauta-Gygax stain for degeneration of nerve endings.[51]

The increasing demand for more sensitive methods for studying biologically active substances has played a major role in developing methods such as fluorescence and immunofluorescence for the demonstration of biogenic monoamines (dopamine, noradrenaline, 5-hydroxytryptamine) and histamine. In the 1970s, immunocytochemistry emerged as a powerful method for identifying structures and tracing pathways in the nervous system. The visualization of antigen-antibody complexes was developed first for light microscopy, but later, techniques were developed for electron microscopy.[49] Immunocytochemistry now plays a fundamental role in the neuroanatomic and histochemical analysis of the CNS.

COUNTING OF NEURONS

Ever since the neuron was recognized as a cell unit in the CNS, attempts have been made to estimate the number of neurons in the system's different parts. Neuronal counting in normal and pathologic central auditory systems, specifically in the cochlear nuclei, has increased in importance since the development of techniques for CNS implantation for the hearing-impaired.

Different methods have been designed, but the most accepted method is that of direct counting under the microscope.[52] The specimen is embedded in paraffin or celloidin, sectioned at 5 to 40 μm in thickness, stained, and examined under the microscope. Four sampling methods for neuronal counts can be used: 1) total count method, 2) systematic section method, 3) random section method, and 4) sample and volume method.

The total count method consists of counting all neurons or neuronal nuclei in serial sections. This is the most accurate approximation of the total neuronal population of the nucleus studied.

The systematic section method consists of three types of sampling: 1) a systematic sample of periodic sections through the structure, 2) a random sample of sections through the structure, and 3) systematic or random samples of neuron population per unit volume together with an estimate of the volume of the structure.

The random section method consists of determining the number of cells per unit volume and multiplying this figure by the total volume.

The sample and volume method incorporates a volume determination in the population estimate. Utilizing area and volume estimates of the structure, this method can be applied in two ways: 1) by taking small samples of neuronal populations throughout the structure and 2) by taking total neuronal counts in each section studied. First, however, an estimate of the volume must be obtained. Finally, a computerized image analysis with appropriate programming may reduce the time in neuronal counting.

DISCUSSION

In summary, the Europeans (European Concerted Action Project) have brought together a number of collaborating laboratories to provide investigators with a centralized data base for sharing of information. In Japan there are approximately 15 laboratories, three of which are actively procuring specimens. In the United States, there are between eight and ten laboratories actively procuring a significant number of temporal bones. However, the workshop conferees agreed that procurement of temporal bones, maintenance of temporal bone histopathologic laboratories, and training of fellows in temporal bone pathology vary with the interest of the director of the laboratory (and the chairperson of the department). Therefore, the productivity and activity of laboratories vary. It was agreed that valuable collections of temporal bone pathologic specimens must not be lost through neglect.

More centers should be harvesting the entire brain, or at least those portions of the brain that include the central auditory and vestibular systems along with the temporal bone, since there is a great need for understanding the normative data and pathologic findings of these pathways.

NEWER TECHNIQUES

TECHNIQUES FOR REMOVAL AND PROCESSING OF TEMPORAL BONE SPECIMENS, INCLUDING EUSTACHIAN TUBE AND ACCESSORY STRUCTURES

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INTRODUCTION

Since Schuknecht[43] described the classic method that we use in our laboratory for removing temporal bones, there have been few variations.[44,53,54] One of them is our method of obtaining specimens that include not only the petrous portion of the temporal bone and the structures in the sphenoid bone such as the oval foramen and spinous foramen, but also some of the structures in the upper part of the parapharyngeal space and the infratemporal fossa. With this method, we can study the eustachian tube (ET) and its cartilage and glands, the tensor veli palatini muscle (TVPM), the levator veli palatini muscle (LVPM), the pterygoid plate, the lateral and medial pterygoid muscles, the third branch of the trigeminal nerve, the internal carotid artery, and the internal jugular vein. Histopathologic study of these specimens is clinically important, particularly for studying otitis media in association with ET malfunction, and also for studying extensive invasion of tumors in the nasopharynx and/or parotid gland into the parapharyngeal space and/or infratemporal fossa. This paper describes the techniques we now use to remove and process such specimens.[54]

SPECIMEN REMOVAL

The specimen is separated from the skull by five vertical cuts in the floor of the cranial vault with a Stryker saw. The first vertical cut is made in the coronal plane, near the anterior margin of the lesser wing of the sphenoid bone, and extends from the midline to the medial end of the lateral third of the ala minor. The second vertical cut is made in the sagittal plane in the midline, from the body of the sphenoid through the hypophyseal fossa, dorsum sellae, and clivus to the spheno-occipital synchondrosis. At this time, we cut the dura covering the sigmoid sinus to add the endolymphatic sac to the specimen. Then the third vertical cut is made in the axial plane; it is begun at the posterior end of the second cut and is extended through the petro-occipital suture and jugular foramen, to end near the marginal area between the transverse sinus and the sigmoid sinus. The fourth vertical cut is begun just parallel to and close to the medial side of the squamous portion of the temporal bone; this cut connects the lateral edge of the third cut to the point on the coronal plane at which the foramen spinosum is located. The final vertical cut connects the lateral end of the first cut and the anterior edge of the fourth cut (Fig 6).

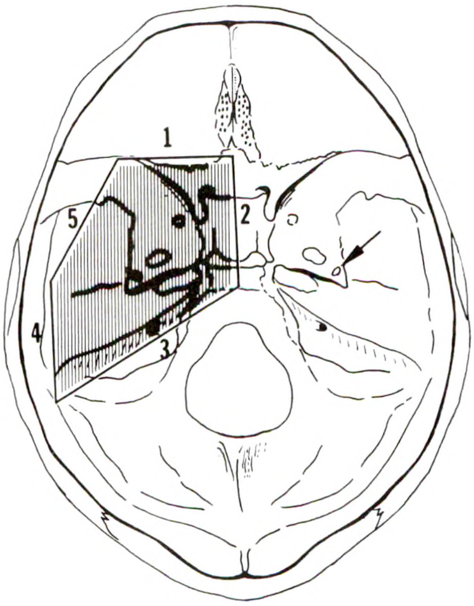

Fig 6. Area on skull base from which left temporal bone specimen, including eustachian tube and its accessory structures, will be removed. Numbers indicate vertical cuts made in skull base. Arrow — foramen spinosum.

After these cuts have been made in the skull base, we use a special long-bladed saw we developed (Fig 7) to sever the palatine bone, the pterygoid process of the sphenoid bone, and the posterior end of the alveolar process of the maxillary bone from the anterior cranial fossa to the oral cavity. We use the saw along the first cut and along the anterior half of the second and fifth cuts, placing it deep enough to reach the mucous membrane of the palate.

Next, we insert straight, long scissors through the anterior half of the slitlike space under the anterior half of the

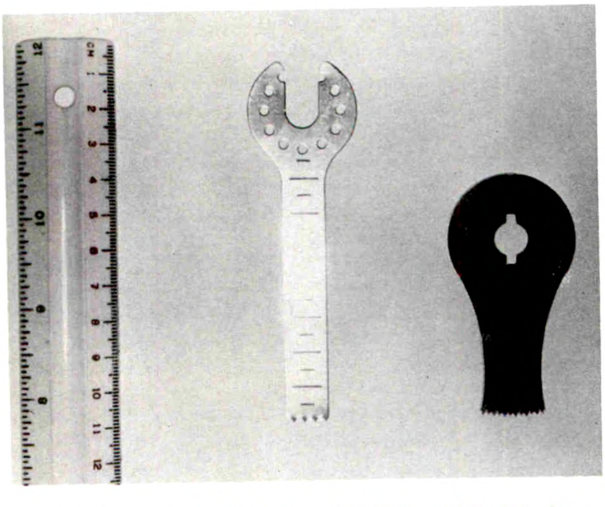

Fig 7. Long blade (left) and regular blade (right) of Stryker saw.

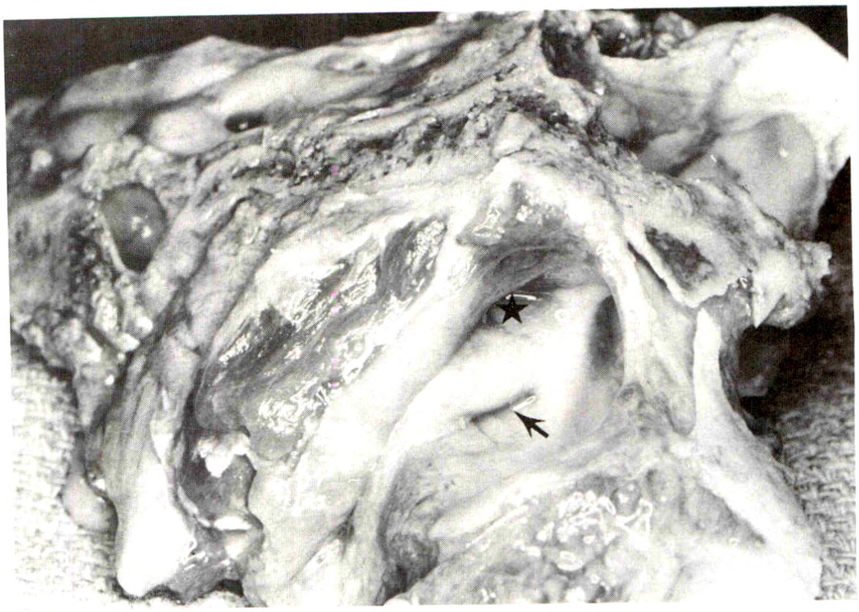

Fig 8. Specimen removed by technique described. Arrow — orifice of eustachian tube, star — Rosenmüller's fossa.

temporal bone specimen and cut the mucous membranes of the hard and soft palates so they are not damaged when the bone is removed. This requires manual palpation so as not to damage the oral cavity. Thus, a pair of mouth openers is used to force the mouth open for observation and palpation, and the operator palpates the soft and hard palates' buccal mucosa while the membranes are severed.

To separate the other soft tissues from the specimen, the specimen is grasped firmly in a noncritical area with a lion-jawed forceps and pulled into the cranial cavity. Then curved scissors are used to cut the soft tissues as far away from the specimen as possible.

To prepare the cadaver for embalming, the internal maxillary and internal carotid arteries must be tied securely (so that when fixative solution is injected into the common carotid artery through the opened chest cavity there are no leaks). The external auditory meatus should be sutured, and the area from which the specimen was removed packed tightly with gauze.

A specimen properly removed in the manner just described (Fig 8) should include the entire inner ear, endolymphatic sac, internal auditory canal, middle ear, mastoid, tympanic membrane, ET, ET cartilage, ET gland, TVPM, LVPM, pterygoid process, pterygoid hamulus, lateral and medial pterygoid muscles, spinous foramen of the sphenoid bone, oval foramen, third branch of the trigeminal nerve and gasserian ganglion, otic ganglion, middle meningeal artery, internal maxillary artery, internal carotid artery, internal jugular vein, and soft and hard palates. Such specimens are much larger than the usual temporal bone specimen, so to avoid disfiguration of the cadaver, the following points should be kept in mind.

1. Remove only one specimen from each cadaver.
2. If either side of the specimen is equally acceptable for study, remove the left specimen. This will reduce the possibility of problems with embalming, since the right side of a cadaver's face is viewed.
3. During removal of the specimens, palpate the mandible laterally and caudally to prevent accidental injury to the facial skin by the saw, chisel, or scissors.

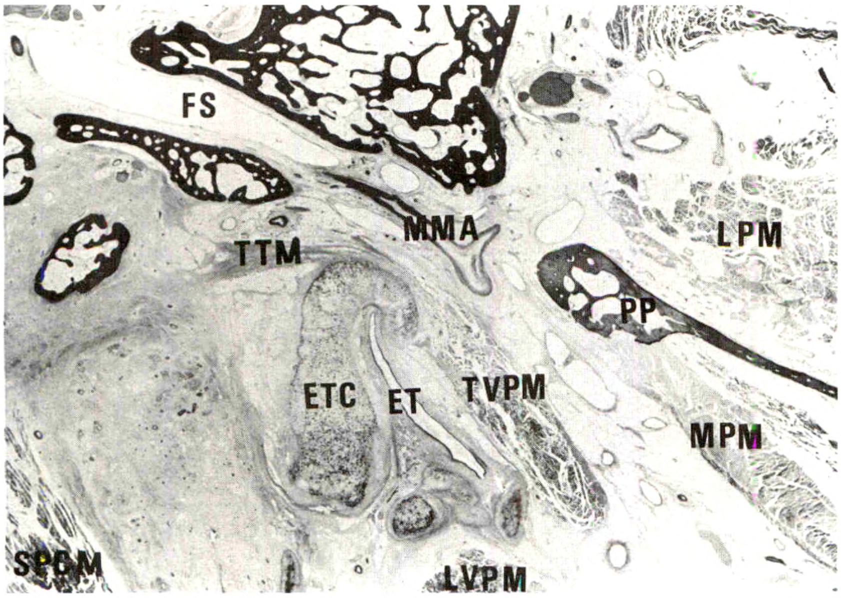

Fig 9. Vertical histologic section. ET — eustachian tube lumen, ETC — midcartilaginous portion of eustachian tube cartilage, FS — foramen spinosum, LPM — lateral pterygoid muscle, LVPM — levator veli palatini muscle, MMA — middle meningeal artery, MPM — medial pterygoid muscle, PP — pterygoid plate, TVPM — tensor veli palatini muscle, SPCM — superior pharyngeal constrictor muscle, TTM — tendon of tensor tympani muscle.

HISTOLOGIC PROCESSING

These large specimens are processed in the same way as temporal bone specimens. After fixation in 10% formalin solution for 2 weeks at room temperature, 5% trichloroacetic acid solution is used for decalcification. When the end point of decalcification is reached, as determined by a chemical test, the acid solution is neutralized by 5% sodium sulfate solution. Specimens then are dehydrated by placement in increasing concentrations of ethanol, and then an ether/ethanol solution. The specimen is embedded in celloidin and hardened by desiccation with chloroform. We then make reference marks in the celloidin block for computer-aided three-dimensional reconstruction and measurement of structures.

After vertical sectioning of the specimen, usually at 20 μm, a tracer set of sections is stained with hematoxylin and eosin, mounted on clear glass microscope slides, placed in order of cutting, and labeled (Fig 9). The rest of the sections are stored in 80% ethanol for later staining and histologic study as required.

COMMENTS

We have used this technique[54] without any particular problem since 1981, and have collected and studied 125 temporal bone specimens with structures such as the ET and its muscles. Although we are continuing to enlarge our collection, we have obtained enough specimens to date of various ages (24 fetal weeks to 85 years) to permit us to describe postnatal development[55] and anatomy (unpublished observations) of the ET in some detail. We also have examined the ET in such specimens from patients with cleft palate[56] and have examined the temporal bones of individuals with head and neck tumors.[57] Because the specimens include the entire ET with its accessory structures and the middle ear, antrum, mastoid air cells, and entire portion of the inner ear, we can look for interrelations between abnormalities of these structures when major pathologic conditions are present.

Acquiring large specimens such as those described in this paper is more difficult than acquiring ordinary temporal bone specimens. In addition, processing large specimens is time-consuming and expensive; this is perhaps why our collection is the only one large enough to permit histologic study on a meaningful sample size.

We hope that as more temporal bone specimens that include structures in the parapharyngeal space and the infratemporal fossa are collected and studied by us and others, much new knowledge will be gained. In particular, we need to find out more about how ET malfunction relates to otitis media, and the changes that occur with extensive nasopharyngeal and/or parotid gland tumor invasion into the parapharyngeal space and the infratemporal fossa. Such new knowledge is essential to improved care for individuals with these disorders.

HARVESTING AND FIXING HUMAN TEMPORAL BONES

RAUL HINOJOSA, MD

Supported in part by grant DC 00301 from the National Institutes of Health/National Institute on Deafness and Other Communication Disorders.

FIXATION FOR LIGHT MICROSCOPY

The routine fixation consists of immersing the temporal bones in cold 20% formalin, as soon as possible after death, for 24 hours in a refrigerator. Next day the bones are transferred to cold 10% formalin. The cold fixative is changed daily for 5 days, maintained in the refrigerator, and finally changed to 10% formalin at room temperature for another 10 days. The temporal bones can be stored indefinitely in the same fixative solution.[58]

Other fixatives used are Heidenhain-Susa, 4% paraformaldehyde in buffer, and 2.5% glutaraldehyde in buffer. For immunologic studies a solution consisting of 10 mL of 40% formaldehyde, 6 g of mercuric chloride, 5 mL of glacial acetic acid, and distilled water to a volume of 100 mL is being used.[59] The technique of opening the labyrinth before immersion fixation has been abandoned.

PERFUSION FIXATION FOR LIGHT AND ELECTRON MICROSCOPY

The best fixation is obtained by perfusing the fixative solution through the perilymphatic spaces as soon as possible after death of the patient. Once perfused, the temporal bones can remain in situ for several hours, if necessary, until removal at the time of autopsy.

The technique for perilymphatic perfusion is as follows. An ear speculum is placed in the external auditory meatus. Viewed through an operating microscope, the upper portion of the tympanic membrane is cut with a knife and folded forward. With a curette a bony overhang is removed in order to expose the oval and round windows. The incus is displaced to expose the footplate of the stapes. The round window membrane is perforated with a small hook very carefully in order not to damage the osseous spiral lamina in the round window region.[60] A glass pipette 150 to 250 μm in diameter (or a flattened needle) is mounted in a micromanipulator and introduced through a small hole (150 to 250 μm in diameter) in the footplate of the stapes. The pipette is connected through a polyethylene tube to a syringe containing 30 mL of the fixative. The syringe is mounted on an infusion pump. If cold fixative is needed for perfusion, the syringe can be mounted in a specially designed copper container filled with ice.[61] The fluid is introduced at a rate of about 0.5 mL per minute. If a pump is not available, the injection can be done by hand at the same rate. The round window area should be monitored to observe whether the fixative is flowing through. A gentle aspiration near the round window niche is necessary to remove the excess of fixative.

If the temporal bones are not going to be removed immediately after perfusion, the middle ear should be packed with gauze soaked with the fixative in order to prevent the fixative from leaking out of the inner ear.

After the temporal bones are removed at autopsy, they are immersed in the same fixative. At this step the perilymphatic perfusion is repeated several times for a period of 1 to 2 hours. If the fixative is other than osmium tetroxide, the specimens can remain in the same fixative for up to 12 to 24 hours in a refrigerator. The specimens can be trimmed in the fixative or after being washed and transferred to 70% alcohol. The excess bone around the cochlea is removed with a rongeur and drills until only a thin bony shell is left around the cochlea and the cochlear turns are outlined. In order to facilitate the penetration of fluids and embedding medium, several small openings are made in all turns and at the apex of the cochlea, with care taken not to damage the spiral ligament or any other structure.

If intravascular perfusion with formalin or any other fixative is used to achieve a good fixation of the brain, the intralabyrinthine perfusion of the ear should be carried out first and the oval and round windows sealed with dental wax during the vascular perfusion.[60]

FIXATIVES

The more frequent fixatives used are as follows.[42] Osmium tetroxide is used as a primary fixative in a solution that varies from 1% to 2.5% in phosphate, cacodylate, or collidine buffer. After removal, the temporal bones can be immersed for up to 2 hours in the same fixative. The specimens can be washed in buffer or transferred directly into 70% alcohol.

Glutaraldehyde alone is used in concentrations that vary from 1.5% to 6.5%, mainly in phosphate buffer. A combination of 2.5% glutaraldehyde and 2% paraformaldehyde in cacodylate buffer also is often used. After a time that varies from 1 to 24 hours, the specimens fixed in aldehydes are washed in buffer and dehydrated in alcohols before embedding.

MICRODISSECTION IN HUMAN TEMPORAL BONE MORPHOLOGY

CHARLES G. WRIGHT, PHD; WILLIAM L. MEYERHOFF, MD, PHD

INTRODUCTION

The two methods most often used for histologic study of the human temporal bone are serial sectioning and microdissection. The first of these basic approaches usually involves light microscopic study of appropriately stained cross sections cut from decalcified temporal bones embedded in celloidin. The second method employs dissection of intact, unembedded material to obtain tissue specimens that subsequently are processed for either light or electron microscopic evaluation.

Each of these approaches has its specific advantages and limitations and both provide different and, to a significant extent, complementary views of middle and inner ear anatomy. It is therefore very beneficial to have both techniques available for use in the temporal bone laboratory.

Microdissection offers a direct, three-dimensional perspective that is not possible with conventional serial sectioning. It also provides great flexibility in the choice of procedures used for final tissue evaluation, since specimens obtained by dissection later can be studied as surface preparations, embedded in epoxy resin for sectioning, or processed for electron microscopy. This article will outline some major applications of the microdissection method as currently employed in the authors' laboratory.

MICRODISSECTION AND SURFACE PREPARATIONS

A detailed description of the microdissection technique, including discussion of appropriate fixation procedures, has been provided by Hawkins and Johnsson,[62] and therefore only a brief summary of the technical aspects of the method is necessary here. Temporal bones to be processed for microdissection are obtained as described by Schuknecht,[43] by use of a bone plug trephine. After examination and removal of the tympanic membrane (which may be saved for histologic study), the ossicular chain and middle ear cavity are examined carefully with the aid of a surgical microscope, and any abnormalities that may be present are documented photographically. The inner ears then are perfused with osmium tetroxide, glutaraldehyde, or paraformaldehyde for fixation of the membranous labyrinth (2.5% glutaraldehyde in veronal acetate buffer is used routinely in our laboratory).

If glutaraldehyde or paraformaldehyde is used as the primary fixative, the membranous structures of the inner ear must be stained subsequently by perilymphatic perfusion with osmium. After staining, the otic capsule is drilled to a thin shell, and the remaining bone is removed to expose the membranous labyrinth, as illustrated in Fig 10. At this stage, abnormalities in shape and/or length of the cochlear duct or semicircular canals are readily apparent and can be photographed with low power magnification. Also, since the cochlear duct remains intact after removal of the otic capsule, it is possible to observe the position of Reissner's membrane reliably and note any distention or collapse that may have occurred in connection with inner ear disease.

After examination and photographic documentation of the intact specimen with the stereomicroscope, the spiral ligament and stria vascularis are removed, and the organ of Corti is divided into segments and separated from the modiolus. These tissue specimens then may be mounted in glycerol and viewed by light microscopy as surface preparations, embedded in plastic for sectioning, or prepared for scanning electron microscopy.

An important advantage of microdissection is that it permits detailed, quantitative study of the entire length of the organ of Corti and stria vascularis. The investigator need not rely on "reconstruction" of the cochlear anatomy from every tenth tissue section, as is commonly done with celloidin-embedded temporal bones. Even in cases in which postmortem autolysis is fairly far advanced, the reticular lamina of the organ of Corti tends to remain intact, permitting accurate assessment of the hair cell population in surface preparations, as illustrated in Fig 11. As with

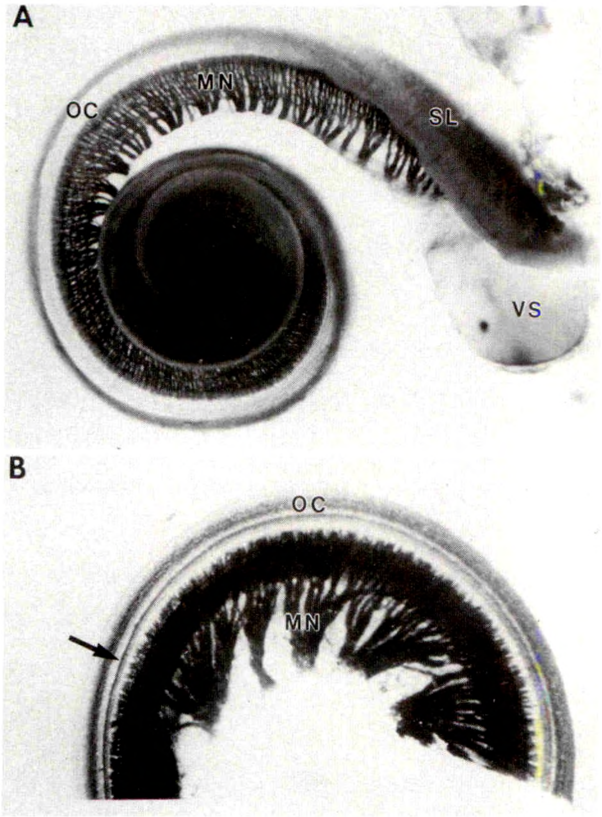

Fig 10. Cochlear dissection. OC — organ of Corti, MN — myelinated fibers. A) Immediately after removal of bone surrounding membranous labyrinth and seen at low magnification (original x15). Myelinated fibers of auditory nerve are well displayed in osseous spiral lamina of basal turn. SL — spiral ligament, VS — vestibule. B) Low power micrograph of surface preparation of OC taken from upper middle cochlear turn (original x31). Dark band (arrow) in OC indicates pillar cell headplates overlying tunnel of Corti, which lies between inner and outer hair cell areas.

similar preparations from experimental animals, it is possible to make hair cell counts on human specimens and construct cytocochleograms on which the extent and location of any sensory cell loss is plotted for the whole length of the cochlear duct. In addition, areas of degeneration or atrophy of the stria vascularis are easily identifiable in surface preparations. Corresponding segments of the stria and organ of Corti can be mounted together on the same slide, so as to allow accurate spatial correlation of lesions involving the hair cells and stria.

Auditory nerve fiber loss associated with end organ disease also can be assessed by this method, since the osseous spiral lamina is included with the organ of Corti in surface preparation specimens (Fig 10). Osmium stains the myelinated nerve fibers darkly, so that thinning or loss of the peripheral innervation is readily detectable in the area of the osseous lamina. In cases in which it is of interest to evaluate the spiral ganglion cell population, the modiolus can be decalcified and embedded for sectioning to permit study of the ganglion cells in much the same way as in conventional temporal bone sections.

Microdissection is also a very useful method for examination of the vestibular organs of the inner ear. In the study of vestibular disorders one occasionally encounters striking deformities in overall shape and size of the various parts of the vestibular apparatus, particularly when dealing with developmental anomalies of the temporal bone. Microdissection is especially well suited for study of such abnormalities because the entire system can be kept intact, viewed in three dimensions, and photographed with the dissection microscope. This approach avoids the difficulties of interpretation that may occur in the reconstruction of complex three-dimensional anatomy from sequential temporal bone sections.

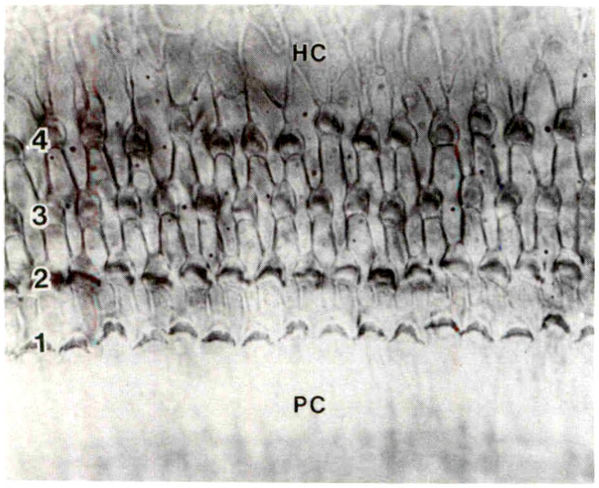

Fig 11. Light micrograph of outer hair cell area in surface preparation from lower apical cochlear turn (original x600). As is occasionally true in human material, four rows of outer hair cells (1, 2, 3, 4) are present. At level of focus illustrated here, stereocilia are visible on first and second rows of hair cells. PC — pillar cell area, HC — Hensen's cells.

Because of their thickness and irregular shape, the sensory epithelia of the vestibular apparatus are somewhat more difficult than the cochlear structures to process as surface preparations. However, with care, the neuroepithelia can be peeled away from the underlying tissue and mounted in glycerol for light microscopic survey of the hair cell population. In the case of the maculae, the otoconial membranes and myelinated nerve fiber network

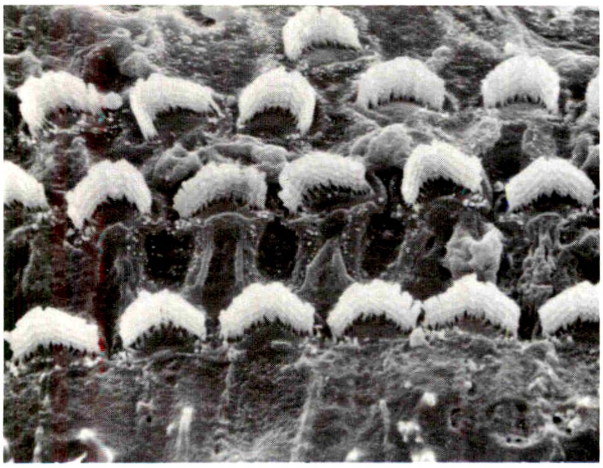

Fig 12. Scanning electron micrograph showing stereocilia on outer hair cells of middle cochlear turn (original x1,500). Specimen was prepared by critical point drying and was sputter-coated with gold-palladium.

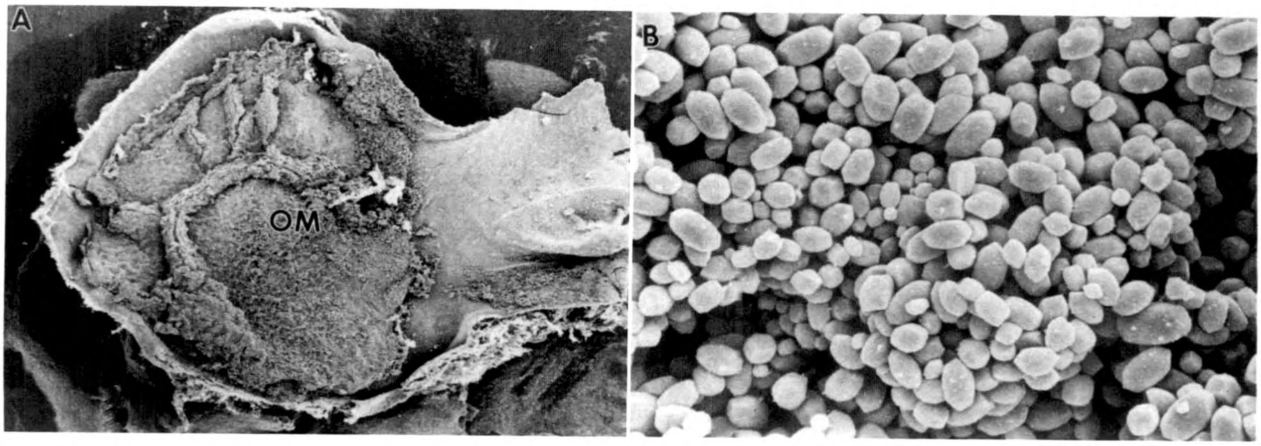

Fig 13. A) Low power scanning electron micrograph of human utricular macula with otoconial membrane (OM) in place on macular surface (original x27). B) Higher power view of otoconial membrane showing normal utricular otoconia from newborn infant (original x2,000).

underlying the sensory epithelium can be mounted separately on slides for light microscopic examination.

PLASTIC EMBEDDING AND TRANSMISSION ELECTRON MICROSCOPY

During examination of surface preparations with the compound microscope, the investigator is by no means limited to viewing the tissue surface. Valuable information regarding the various cellular and vascular constituents of tissue specimens can be obtained from surface preparations by careful adjustment of the level of focus.

Microscopic evaluation of specimens obtained in the course of microdissection is also quite feasible with sectioned material. Selected portions of the organ of Corti, stria vascularis, vestibular neuroepithelia, and endolymphatic sac can be embedded in epoxy resin and sectioned at 1 to 2 μm thickness for high resolution light microscopy. This method is especially advantageous for study of the hair cell and nerve fiber populations of the cristae and maculae, since as mentioned above, these organs are more difficult to process as surface preparations.

In cases in which the postmortem interval before tissue fixation is short (within 1 to 2 hours), thin sections for transmission electron microscopy may be cut from plastic-embedded specimens. These sections occasionally prove to be very informative in spite of the presence of various degrees of postmortem autolysis. Artifacts associated with autolysis can be reduced significantly if fixative is introduced into the middle and/or inner ear via a tympanotomy approach shortly after death and before the time of autopsy, as has been shown by Bredberg,[63] Wright,[64] and others.

SCANNING ELECTRON MICROSCOPY

Details of normal anatomy and fine structural pathologic changes affecting stereocilia and other surface structures sometimes can be evaluated successfully in human material by means of scanning electron microscopy (SEM). Surface structures of the organ of Corti and vestibular neuroepithelia tend to remain relatively well preserved for SEM if the postmortem interval before fixation is not excessively long. As can be seen in Fig 12, satisfactory results have been obtained in our laboratory with tissue specimens dehydrated to 100% ethyl alcohol, critical point dried with use of carbon dioxide as the transition fluid, and sputter-coated with gold-palladium. The preparation of human cochlear tissues for SEM and identification of postmortem artifacts has been well discussed in a series of papers by A. Wright of the University of Liverpool.[65-66] We have found SEM of the human organ of Corti to be valuable in the study of early structural changes secondary to drug toxicity (as, for example, following cisplatin administration).[67] The technique also can be applied advantageously in the assessment of developmental defects of the inner ear.[68]

Finally, SEM is an informative method for detailed study of the accessory sensory structures of the membranous labyrinth such as the tectorial membrane, cupulae, and otoconial membranes.[69] Previous work in our laboratory has focused on investigation of the otoconial membrane of the human vestibular apparatus.[70-72] Recent studies have shown that these structures may undergo a variety of pathologic changes in disease conditions affecting the inner ear. The combination of microdissection and scanning electron microscopy has proved to be ideal for investigation of the normal structure, fetal development, and disorders of human otoconia. By use of microdissection, it is possible to avoid entirely the processing procedures that decalcify the otoconia and radically alter their morphology. Within a few hours after temporal bones are obtained at autopsy, the maculae can be dissected intact from the saccule and utricle and critical point dried with the otoconial membranes in place as shown in Fig 13. Alternatively, the otoconial membranes may be lifted off the maculae during microdissection and dried on foil tabs. The maculae then can be processed separately for SEM study of the neuroepithelia and evaluation of possible hair cell loss or other disease.

The composition of fixative solutions used in temporal bone processing becomes an important consideration if studies of the otoconia are planned. All solutions that come into contact with the specimens must be maintained at pH 7 or higher, since at acid pH the calcium carbonate otoconial crystals will undergo partial dissolution. Either aldehyde fixatives or osmium tetroxide may be used for preservation of the macular structures. However, phosphate-based buffers should be avoided when preparing fixatives, because phosphate will replace carbonate in the otoconia, forming calcium phosphate crystals that drastically change the normal morphology of the otoconia.

Changes in mineral composition of human otoconia now are known to occur in association with several types of ear disease. Radiographic microanalysis and x-ray diffraction methods can be used to determine the distribution of chemical elements and identify the mineral constituents of otoconial samples obtained by microdissection.[71,72] These techniques allow the investigator to identify specific changes in chemical and crystallographic properties associated with alterations of morphology that may be found during SEM study.

SURFACE PREPARATIONS FOR HUMAN TEMPORAL BONE STUDIES

JOSEPH E. HAWKINS, PHD, DSC

Supported by United States Public Health Service Program Project Grants NS 05785 and NS 21440, Research Grant NS 05065, and Food and Drug Administration contract 223-87-6028.

During the past quarter-century, the method of microdissection and surface preparation has come into use for the examination of pathologic changes in the inner ears of human patients, as well as in those of various species of experimental animals ranging from mice to monkeys. Although the comprehensive yet detailed view it offers of the various inner ear tissues at first seemed new and strange to many present-day otologists, it is by no means a new method. The microscopic examination of whole-mount or surface preparations of cochlear tissues dates back at least to Alfonso Corti himself. In his celebrated publication of 1851,[1] he depicted not only the sadly autolyzed and now hardly recognizable cross section of the sensory organ he had discovered, but also a quite respectable surface view of the same structure, with its mosaic pattern clearly defined, as well as the fibrillar components of the basilar membrane (Fig 14). The presence of these "stretched strings," together with the stiff rods of Corti, encouraged Helmholtz in formulating his resonance theory of hearing. In his *Lehre von den Tonempfindungen*,[73] Figures 48 and 51 show surface views of the spiral lamina and basilar membrane borrowed from Hensen.

OTHER EARLY USERS OF SURFACE PREPARATIONS

Among the 19th-century investigators who made surface preparations was Lavdowsky,[74] who illustrated his 1877 publication with a handsome colored lithograph of a portion of the organ of Corti and associated cochlear neurons from the inner ear of a dog (Fig 15). Moos and Steinbrügge[75] of Heidelberg appear to have been the first to examine surface preparations taken from the human inner ear, using them to demonstrate the ramifying pattern of the bundles of myelinated nerve fibers in the osseous lamina. Their drawing (Fig 16) clearly shows the intralaminar spiral fibers,[76] but they interpreted them as anastomotic connections among the radial fibers rather than as a separate group of neurons.

The not-quite-regular mosaic pattern of the human reticular lamina, with its occasional phalangeal scars and supernumerary outer hair cells forming incomplete fourth and fifth rows, was pictured by Retzius[77] in one of his attractive drawings of surface preparations (Fig 17) that are to be found in the second volume of his *Gehörorgan der Wirbelthiere*[77] (1884). At that time he seems to have overlooked the centrosomes of the hair cells and supporting cells. They are displayed clearly, however, in a drawing of the human reticular lamina published in 1901 by Graf Spee[78] (Fig 18). Other leading anatomists of the inner ear in the pre–electron microscopic era, Held[79] of Leipzig and Kolmer[80] of Vienna, used surface preparations from adult human ears to illustrate the structure of the reticular lamina and the cytoarchitecture of Corti's organ. Again, their concern was primarily with normal rather than with pathologic anatomy.

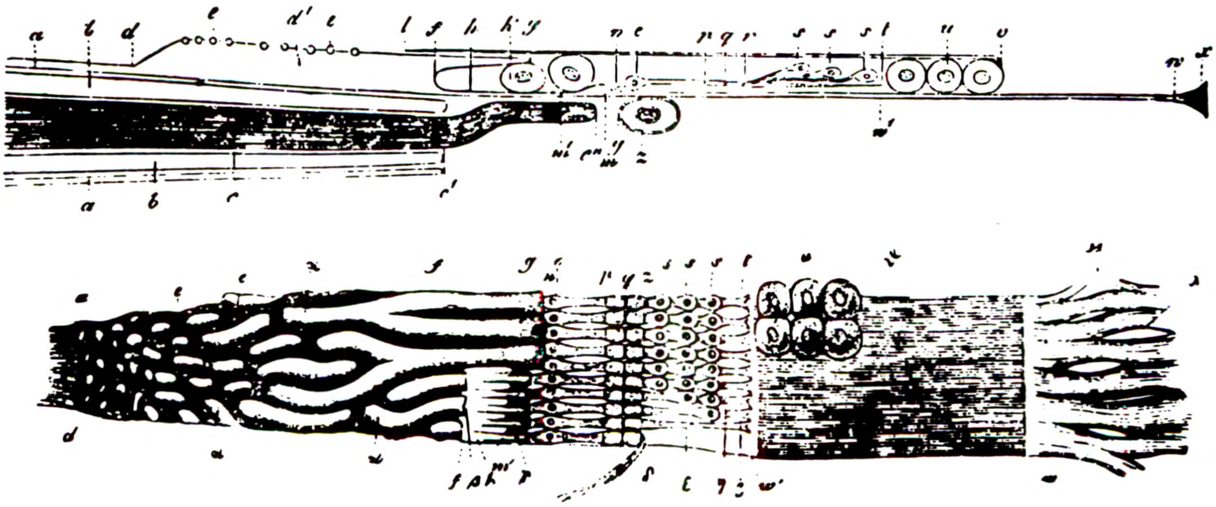

Fig 14. Corti's cross-sectional and surface views of "organ of hearing." (From Corti [1851].[1])

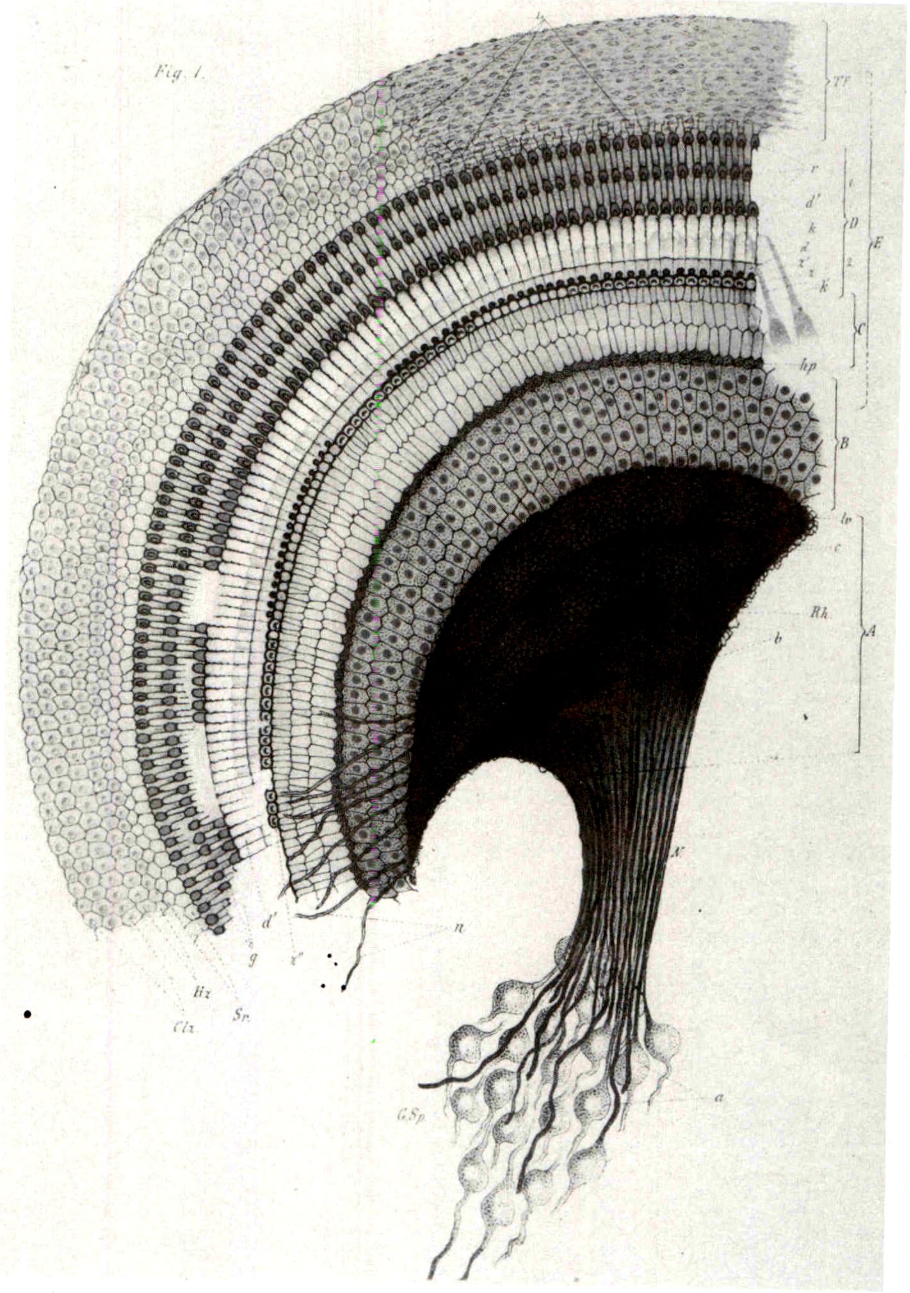

Fig 15. Lavdowsky's surface preparation of segment of apical turn of spiral lamina of adult dog, showing organ of Corti, with cochlear nerve fibers and spiral ganglion cells (Ag2O, OsO4, picrocarmine). (Plate xxxii from Lavdowsky [1877].[74])

NEUBERT'S *HÄUTCHENPRÄPARAT*

The current revival of the method of microdissection and surface preparations may be said to have begun in 1950 with the introduction by Neubert[81] (1950) of his *Häutchenpräparat*, or "membrane preparation," a term he first applied to a specimen taken from the spiral ligament. In his subsequent studies, whole-mounts of the basilar membrane and organ of Corti dissected from the guinea pig cochlea were treated with gallocyanin chrome alum or an appropriate preparation of hematoxylin to stain the nuclei of the hair cells. Swollen or pyknotic nuclei were interpreted as marking the sites of action of acoustic stimuli or ototoxic drugs. Neubert also pointed out the potential value of his *Häutchenpräparat* for extending the statistical work of Retzius on the number of hair cells in relation to supporting cells and for evaluating pathologic and degenerative changes in Corti's organ. He called attention to the time saved by avoiding the long process of decalcification, embedding, and preparing serial sections. He even mentioned that he had succeeded in making similar preparations from human inner ears, but he seems not to have pursued this matter further.[82]

The *Häutchenpräparat* has been used extensively by Beck and his colleagues for experimental studies of physiologic and pathologic processes in the cochlea. The term "cytocochleogram" first appears in relation to a quantitative evaluation of the ototoxic action of streptomycin in the guinea pig cochlea by Beck and Holz.[83]

OSMIUM TETROXIDE FIXATION AND PHASE-CONTRAST MICROSCOPY

For visualizing the structure of Corti's organ and other cochlear tissues as flat or surface preparations, Engström et al[84] chose osmium tetroxide for fixation and staining.

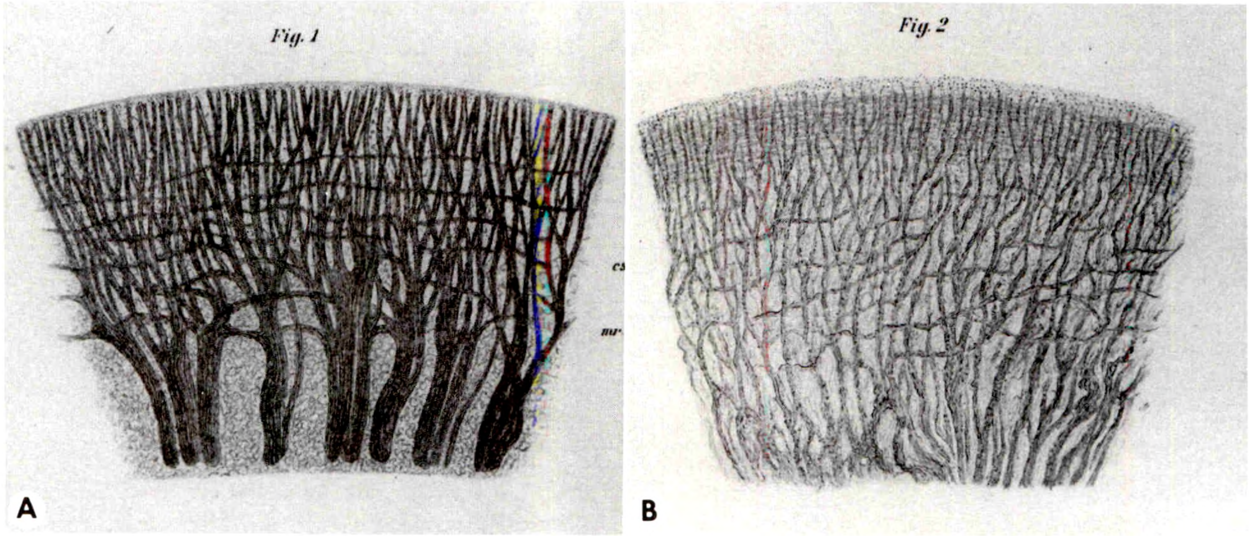

Fig 16. Moos and Steinbrügge's surface preparations of segments of osseous spiral laminae from human ears. A) Normal cochlear neural pattern in 19-year-old man with normal hearing. B) Thin, sparse nerve fibers in 63-year-old man with constant tinnitus and hearing impairment of sudden onset. Authors identify intralaminar spiral fibers incorrectly as anastomoses between fiber bundles. (Plate i from Moos and Steinbrügge [1881].[75])

They mounted their specimens in glycerol and viewed them by phase-contrast illumination. Their version of the *Häutchenpräparat* not only provides a clear view of the mosaic pattern of the reticular lamina, but permits an in-depth examination of the bodies of the sensory and supporting cells, the myelinated and unmyelinated nerve fibers, the basilar membrane, and the spiral vessels beneath. Representative photomicrographs illustrating normal cochlear cytoarchitecture in the guinea pig are shown by Hawkins[85] and by Engström et al.[86] Detailed descriptions of the technique have been published by the latter authors[86] for the guinea pig, and by Hawkins and Johnsson[62] for the guinea pig and monkey. This method has been used for studies in animal models of the otopathologic changes associated not only with ototoxicity and injury by noise, but also with aging[87] and labyrinthine hydrops.[88]

HUMAN TEMPORAL BONE STUDIES

The technique for preparation of the human temporal bone is similar to that recommended for the monkey.[62] Otopathologic reports based on microdissections and surface preparations of human temporal bones first were published in 1965 by Bredberg et al[89] and in 1967 by

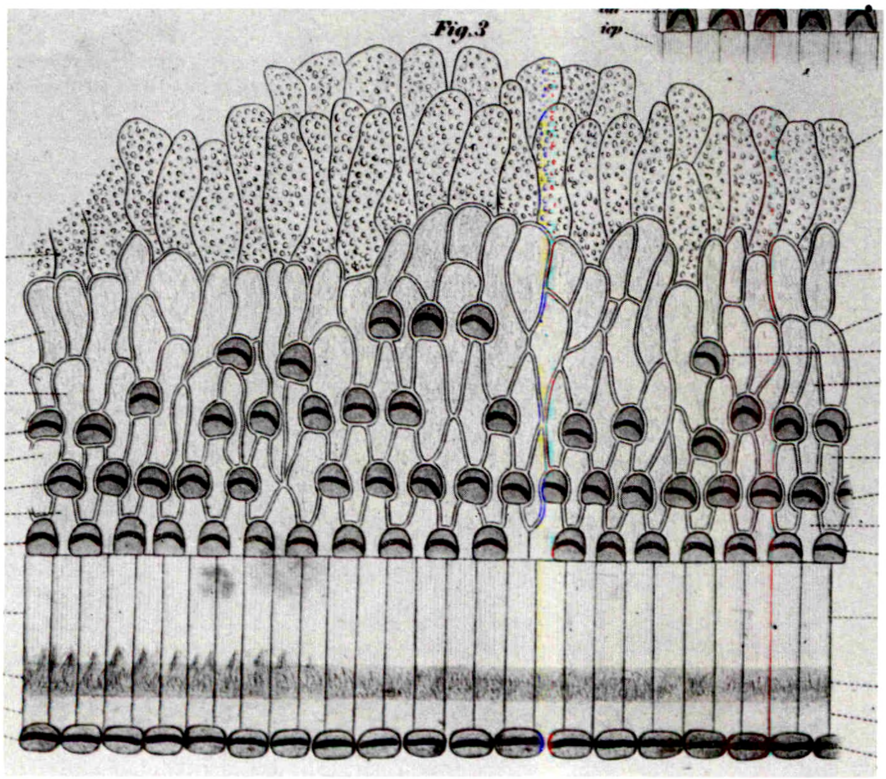

Fig 17. Retzius's drawing of surface preparation of adult human organ of Corti from second cochlear turn, showing characteristic mosaic pattern of reticular lamina, with occasional missing outer hair cells and hints of fourth and fifth rows. (Plate xxxvii from Retzius [1884].[77])

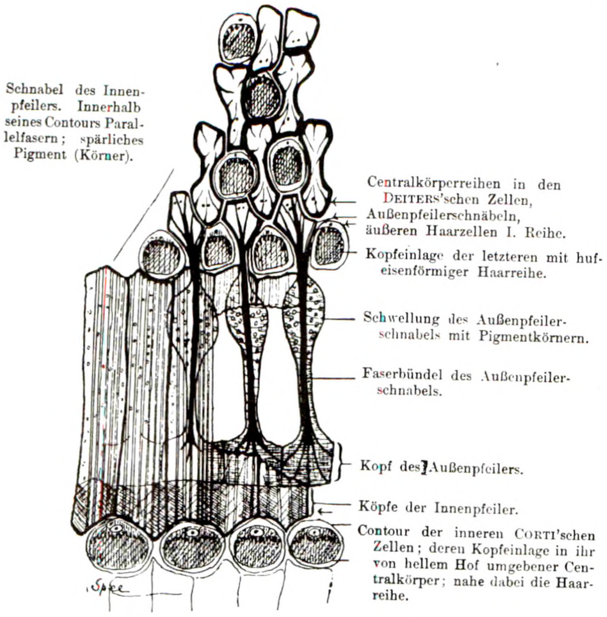
Schnabel des Innenpfeilers. Innerhalb seines Contours Parallelfasern; spärliches Pigment (Körner).
Centralkörperreihen in den DEITERS'schen Zellen,
Außenpfeilerschnäbeln,
äußeren Haarzellen I. Reihe.
Kopfeinlage der letzteren mit hufeisenförmiger Haarreihe.
Schwellung des Außenpfeilerschnabels mit Pigmentkörnern.
Faserbündel des Außenpfeilerschnabels.
Kopf des Außenpfeilers.
Köpfe der Innenpfeiler.
Contour der inneren CORTI'schen Zellen; deren Kopfeinlage in ihr von hellem Hof umgebener Centralkörper; nahe dabei die Haarreihe.
Spee

Fig 18. Graf Spee's drawing of surface preparation showing cytoarchitecture of reticular lamina of human organ of Corti and centrosomes of hair cells and Deiters' cells. (From Spee [1902].[78(p258)])

Johnsson and Hawkins.[90] A description of Bredberg's valuable findings in his series of 29 fetuses, six infants, and 72 other subjects 1 to 93 years of age appeared the following year.[63] Johnsson and associates since have published a series of papers concerned with otopathologic changes observed in more than 400 pairs of ears, many of them from patients with hearing impairment associated with presbyacusis,[76,91] noise-induced hearing loss,[92] ototoxicity,[93] capsular otosclerosis with hydrops,[94] or other clinical conditions. Further recent examples of contributions to the otopathologic literature based on the examination of surface preparations from human inner ears include, among others, those of Tange[95] in Amsterdam and Wright et al[68] in Dallas.

ADVANTAGES

When compared with the conventional technique of stained serial sections, the method of microdissection and surface preparations offers several important advantages.[90]

1. A pair of human temporal bones can be ready for histologic examination in a week or less, since there is no months-long wait while they are being fixed, decalcified, embedded, cut, stained, and mounted.
2. It affords a "mini-autopsy" of the temporal bone, in which anomalies and pathologic changes such as middle ear defects, hemorrhage, or hydrops can be assessed. Microdissection of the inner ear is particularly valuable in revealing the exact location of a cochlear prosthesis or of newly formed bone in the scala tympani.[96]
3. With the removal of the otic capsule, one has an immediate view in the stereomicroscope of the basilar membrane and organ of Corti and of the myelinated cochlear nerve fibers in the osseous lamina (Fig 19).
4. Viewed with phase-contrast or Nomarski optics, the surface preparations permit a complete, detailed examination of the entire length of the reticular lamina in which hair cells remaining and those replaced by phalangeal scars can be enumerated and tabulated for plotting a cytocochleogram (Figs 20 and 21).
5. Any lesion or degeneration of sensory or neural structures is recognized readily without the need for graphic reconstruction. The observer enjoys an immediate, comprehensive, and reliable impression of the condition of Corti's organ, and the cytocochleogram plotted can be compared with the audiogram.
6. The problem of postmortem changes is minimized, because the mosaic pattern of the reticular lamina is generally well preserved, even when there is autolysis of the bodies of the hair cells beneath it.
7. With phase-contrast optics one can look below the translucent reticular lamina to examine the hair cells, supporting cells, and nerve fiber bundles, as well as the capillaries of the tympanic lip and basilar membrane.
8. The stria vascularis and spiral ligament with their distinctive microvascular systems, as well as Reissner's membrane and the tectorial membrane, can be displayed as surface preparations and examined in detail.

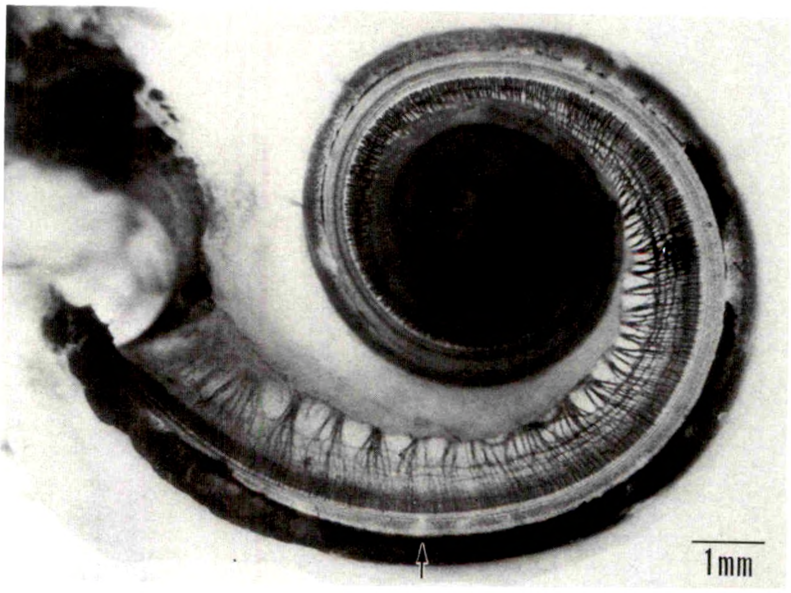

Fig 19. View of osseous lamina and basilar membrane of basal cochlear turn of 92-year-old woman, after removal of otic capsule covering scala vestibuli (OsO_4). Pattern formed by radial and intralaminar spiral neurons of osseous lamina is evident, but fewer nerve fibers are present at lower end of basal turn, where there is patchy degeneration of organ of Corti (arrow). (From Johnsson and Hawkins.[76])

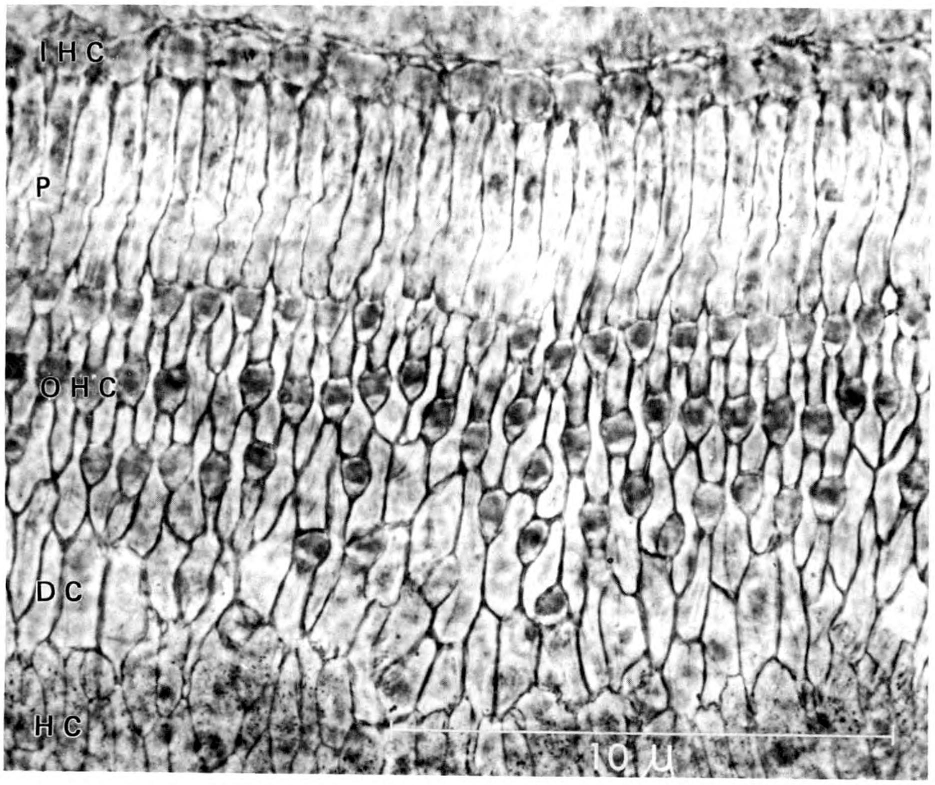

Fig 20. Surface preparation of reticular lamina from middle cochlear turn of 9-year-old boy who died of leukemia. Inner hair cells (IHC) and outer hair cells (OHC) are separated by head plates of inner pillars. Note somewhat irregular mosaic formed by OHC and phalangeal processes of Deiters' cells (DC). HC — Hensen's cell, P — pillar cell. (Reprinted with permission from Johnsson and Hawkins.[90])

9. The maculae, as well as the membranous walls of the utricle and saccule, can be dissected out and studied as whole-mounts.
10. Surface preparations can be embedded in plastic, and thin sections cut for transmission electron microscopic study of specific structures previously identified by light microscopy, or they can be prepared for scanning electron microscopy.
11. After microdissection has been completed, the modiolus can be embedded and serially sectioned for assessment of the spiral ganglion cells and cochlear nerve fibers (Fig 22).
12. Since it provides a direct, three-dimensional view of the osseous and membranous labyrinths and their contents, the method has great educational value for students, resident physicians, and others who wish to enhance their understanding of the anatomy of the temporal bone and inner ear.

DISADVANTAGES

Despite the merits listed above, the method is not without its shortcomings. Chief among these, the following should be noted.

1. The technique of microdissection is labor-intensive and time-consuming, requiring considerable manual skill, practice, patience, and motivation. Hair cell counting and cytocochleogram plotting can be done by a technician after only a moderate investment in training, but it is not a task that can be performed contentedly hour after hour, even with the aid of a computer program.
2. The necessity of making careful photographic records of each temporal bone as key stages in the process of microdissection are completed adds considerably to the time and effort required.
3. The surface preparations mounted in glycerol on glass slides have a tendency eventually to dry out and therefore lack the permanency of serial sections.
4. Although otosclerotic or other lesions of the otic capsule can be examined in the course of micro-dissection,[95] the method does not provide a complete and permanent documentation of their location and extent,

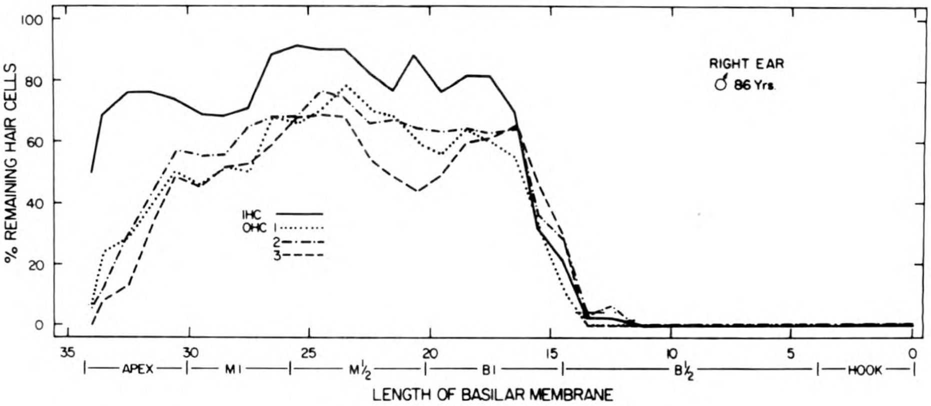

Fig 21. Cytocochleogram for right ear of 86-year-old man, showing complete disappearance of outer hair cells (OHC) and inner hair cells (IHC) and of peripheral processes of cochlear nerve fibers from lower half of basal turn — finding that is not uncommon in presbyacusis. There is also loss of OHC and some IHC at apex. (Reprinted with permission from Hawkins and Johnsson.[91])

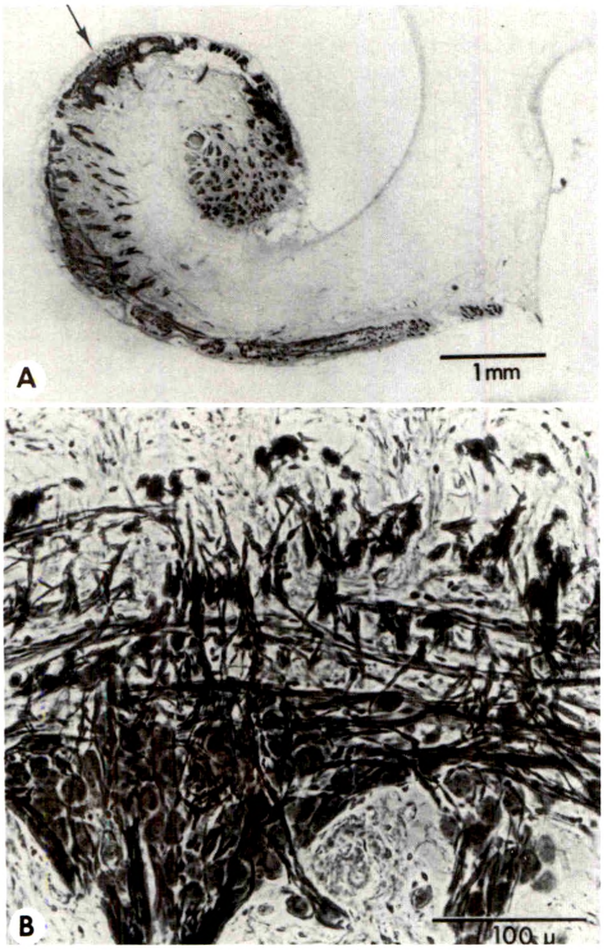

Fig 22. A) Cochlear nerve fibers and spiral ganglion cells in upper basal cochlear turn of 8-month-old girl. After microdissection, modiolus was decalcified, embedded in celloidin, and sectioned approximately in plane of osseous lamina. Arrow — area shown in B. B) Portion of spiral ganglion from same specimen (arrow on A), with cell bodies and peripheral processes of cochlear neurons, as well as longitudinal fibers of intraganglionic spiral bundle (OsO4). (From Hawkins JE Jr, Johnsson L-G. Light microscopic observations of the inner ear in man and monkey. Ann Otol Rhinol Laryngol 1968;77:608-28.)

as does the method of serial sections.

5. The spiral ganglion and the other neural and vascular contents of the modiolus are not available for examination unless the modiolus is embedded and serially sectioned, as indicated above.
6. The ampullar cristae do not lend themselves to satisfactory examination as surface preparations. On the other hand, they can be embedded in Epon or other suitable plastic and examined as thick (1 μm) sections for light microscopy or as thin sections for electron microscopy.
7. Osmium tetroxide, even in 1% solution, is volatile and highly toxic to the skin, eyes, and respiratory tract. Any procedure involving its use must be carried out under a fume hood, and rubber gloves must be worn.

MODIFICATIONS

Over the years, interesting and useful modifications of the method of microdissection and surface preparations have been introduced, most of which involve embedding the specimens in plastic before examining them under the compound microscope. One of these is Spoendlin's block surface method, which has been adapted recently by Spoendlin and Schrott[97] for human inner ear studies. Another is the method of microslicing and staining, as described by Soucek et al.[98] It involves cutting 1.5-mm sections from a fixed but undecalcified temporal bone with a special microslicing machine. Although its availability is still limited, it appears to have considerable promise for detailed examination of cochlear disease.

RECOMMENDATIONS

For routine temporal bone studies, when both ears are available for examination, it seems appropriate to profit by the advantages offered by both the serial section and the surface preparation method. Especially in cases of presbyacusis, ototoxic deafness, noise-induced hearing loss, viral disease, and other conditions in which audiologic tests or previous experience suggest that inner ear changes are likely to be symmetric, one temporal bone should be examined by microdissection and surface preparations, the other by serial sectioning.[68] In this way information about sensory, neural, and vascular disease would be obtained quickly for one ear, and the other ear eventually would become a part of a permanent collection of temporal bone sections.

When a cochlear prosthesis is present, the method of microdissection is indispensable, since there is no necessity for removing the implant (with possible artifactual damage to cochlear tissues) before processing the temporal bone. Rather, microdissection permits the precise position of the electrodes in relation to the cochlear structures to be ascertained by direct inspection, and the implanted array to be photographed in situ.[96]

APPLICATION OF TRANSMISSION ELECTRON MICROSCOPY TO HUMAN OTOPATHOLOGY

JOSEPH B. NADOL, JR, MD

INTRODUCTION

Although relatively few laboratories in Europe and the United States routinely use transmission electron microscopy (TEM) in human otopathology, both the rationale for its use and the ability to obtain human specimens with adequate fixation for TEM have been established. Transmission electron microscopy should provide new data on both normal and pathologic anatomy. There are significant differences in the normal microscopic anatomy of the organ of Corti of the human as compared to the most common animal models used for experiments or physiologic experimentation.[99] The rationale for the use of TEM in pathologic specimens is even more compelling. First, there are disease entities affecting the human temporal bone for which there are no known perfect animal models or counterparts. These include sudden idiopathic sensorineural hearing loss, Meniere's disease, presbycusis (considering the human life span and unique set of environmental, genetic, traumatic, and toxic factors), and otosclerosis, to name only a few of the more common diseases. Second, the accumulated histopathologic data present examples of glaring deficiencies in our ability to correlate disordered function and disordered anatomy at a light microscopic level. This is particularly evident in Meniere's disease and presbycusis. In well-established Meniere's disease the typical audiometric findings include severe sensorineural hearing loss and a marked decrement in speech discrimination. Many authors have pointed out that in such cases there is poor correlation with the light microscopic histopathologic changes in neurosensory structures.[100,101] Similarly, in some cases of presbycusis, the correlation between audiometric data and the histopathologic findings at the light microscopic level is far from perfect.[100,102]

LIMITATIONS ON USE

There are several factors that have contributed to the paucity of information on an ultrastructural level for human pathologic material. The impediments to obtaining satisfactory postmortem human material suitable for light microscopy are magnified for electron microscopy. First, time delays between death and fixation are more critical for electron microscopy and are lengthened by legal requirements and resistance to autopsy by funeral directors and the lay public. However, there is evidence that satisfactory fixation of postmortem human temporal bones can be achieved and that the time between death and fixation is only one factor in determining the quality of fixation.[103] The use of the lateral approach to temporal bone removal in some cases also may shorten delays and allow the retrieval of temporal bones from individuals who do not undergo a conventional hospital-based autopsy.[44]

A second major limitation to the successful application of TEM to the human temporal bone is based on the relative paucity of information on postmortem artifact[103] and of normative data on which to base comparisons of pathologic material. Nevertheless, data in both areas are slowly accruing.[104-107]

The third limitation involves the inherently small sample size that can be studied effectively by TEM. This can be overcome by the combination of TEM with other techniques such as light microscopy, evaluation of surface preparations, and perhaps even postmortem computed tomography. The use of TEM requires the development of different forms of normative data. For example, the traditional method of quantifying spiral ganglion cells by the use of total or segmental counts by serial light microscopic sections poses some difficulty for the simultaneous use of TEM. The establishment of normal ranges for density of spiral ganglion cells at given millimeter segments of the cochlea[108] may prove more useful.

The use of biopsy specimens obtained at surgical procedures presents a special set of problems for electron microscopy, including a host of unknown and uncontrollable surgical factors that may lead to histologic artifacts, such as desiccation, physical trauma, heat injury, and osmolarity problems induced by irrigating solutions. In addition, although electron microscopy has been applied successfully to biopsy specimens in more homogeneous organs such as the liver and kidney, the inner ear presents special problems in obtaining a representative specimen, on both sampling and ethical grounds, in that biopsy of the inner ear may cause auditory and vestibular symptoms.

GENERIC TECHNIQUE FOR PREPARATION OF INNER EAR

The following outline represents steps that I have found critical or effective in maximizing the usefulness of human temporal bone material for electron microscopy. Also indicated are "branch points" in the decision tree, depending upon the special applications to a particular specimen.

The following are steps to reduce delay between death and time of fixation.

1. Perform daily surveillance of the autopsy rooms, pathology department, and patient care units to identify potentially valuable specimens.
2. Perfuse the middle and inner ear via the perilymphatic scalae in the autopsy room or, in special cases, funeral homes or patient care areas well before autopsy or removal of the temporal bone. This is facilitated by dedicated equipment stationed in appropriate locations in the hospital and by maintaining fixation solutions for electron microscopy constantly at the ready.
3. When an autopsy will not be performed, use the lateral temporal bone removal technique[44] to allow retrieval of specimens that otherwise would be lost and to shorten fixation delay.
4. Obtain temporal bones with short postmortem times even if there is no obvious documentation of either normality or otopathology. It is my experience that in many cases, documentation from family members, attending physicians, hearing aid dealers, or military or work records may be obtained in the week subsequent to death and fixation.
5. Increase the "retrieval net" by involving colleagues in other hospitals, departments, and even countries.

Fixation and preparation of specimens should be done as follows.

1. Use the standard buffered aldehyde fixation technique.[105] This may be modified for special applications such as immunocytochemistry.
2. After achieving fixation, review the clinical data to develop a research plan for the particular specimen. This will allow maximum use of the temporal bone material and will determine the next steps in specimen preparation.
3. In most cases, after removal of surface structures of interest, remove the bulk of the temporal bone with rongeurs, and thin the otic capsule with an electric drill. This reduced specimen then may be decalcified in EDTA[105] or microdissected, or postfixed and embedded in situ for subsequent dissection in plastic for surface preparation.[109,110]

The establishment of a readily accessible data file and the cataloging of available specimens from a given temporal bone will establish a library of documented specimens for future use.

EXAMPLES OF NEW DATA OBTAINED

Several authors have contributed to available information on the normal and pathologic structure of the inner ear using electron microscopy. There are significant differences in the innervation patterns of both inner and outer hair cells between the human and the animal models most commonly used for anatomic or physiologic study.[99] Branching of afferent fibers to two or more inner hair cells in the human,[108] the presence of reciprocal synapses at the base of outer hair cells,[111] and differences in the numbers of afferent fibers per hair cell[107] are examples of differences in anatomy between human and animal. Many authors have demonstrated clear differences in the morphology and morphometry of spiral ganglion cells comparing human and animal species.[99] The application of TEM to the round window membrane, middle ear mucosa, endolymphatic duct and sac,[112] vestibular otoconia,[113] stereocilia,[64,104] stria vascularis,[114] intercellular junctions,[115] and developmental anatomy[116] has yielded new data concerning the normal anatomy of the human inner ear.

New data concerning pathologic changes in the inner ear likewise have been achieved, including presbycusis,[102] Meniere's disease,[100,101] Usher's syndrome,[101] ototoxicity,[117] otosclerosis,[118,119] pathologic changes in the endolymphatic duct and sac,[120] disease of the middle ear mucosa, abnormalities of the stria vascularis,[121] and abnormalities in vestibular otoconia,[113] vestibular epithelia,[122-124] and distribution of lipofuscin in the human inner ear.[125]

EXPANDING USEFULNESS AND APPLICATION TO HUMAN OTOPATHOLOGY

The availability of specimens for TEM and associated histologic studies would be enhanced greatly by the following factors.

1. Improved compilation of premortem clinical audiologic and vestibular data on specimens likely or possible to be obtained. This not only would involve expansion of the temporal bone bank concept, but also would be enhanced by shared computer networks of clinical data.
2. Eliminating the bureaucratic delays between death and fixation. Waiting until the immediate postmortem period to discuss permission for obtaining pathologic material that rapidly undergoes autolysis is inherently inefficient and emotionally taxing, both for the physician and for the family members of the deceased. Failure to obtain autopsy permission is more likely to occur in the emotionally charged postmortem period. This issue should be addressed realistically either by legislative action or even by streamlining and enforcing premortem grants of autopsy permission from patient or family, probably in the larger context of general needs for organ procurement. The need for precious pathologic material must take precedence over the statement often coupled with refusal of postmortem examination, "He has suffered enough." Similarly, the continued resistance of funeral directors to the removal of pathologic specimens must be overcome by education and legislation.
3. The expanded use of the lateral temporal bone technique. This will enhance the collection of specimens in cases in which autopsy is not possible or practical.
4. Cataloging and sharing of documented specimens. The inherent limitation of TEM of the very small sample size can be a potential advantage if specimens from the same temporal bone can be shared efficiently by research centers. In addition, as with light microscopy, an "n of one" of any given disorder has only limited value; achieving reproducibility will be enhanced greatly by the sharing of specimens.
5. The compilation of normative data at the electron microscopic level. This will greatly enhance the interpretability of pathologic material.
6. Training of personnel in the retrieval, fixation, and preparation of human temporal bone material for electron microscopy, including the application of newer histologic techniques. This should become more formalized and will require financial support.
7. National public education programs concerning the value of obtaining such material. This will facilitate premortem bequests of temporal bones, provide nonfederal financial support for such research, and reduce the emotional and other resistance to removal of pathologic specimens from the deceased.

COMPUTER-AIDED THREE-DIMENSIONAL RECONSTRUCTION AND MEASUREMENT OF TEMPORAL BONE STRUCTURES

ISAMU SANDO, MD, DMS; AKIRA TAKAGI, MD; HARUO TAKAHASHI, MD

Supported by Research Grant ROI NS 13787 from the National Institutes of Health/National Institute on Deafness and Other Communication Disorders.

INTRODUCTION

We developed computer software to create three-dimensional images of temporal bone structures from two-dimensional histology* sections.[126] This software also enables us to measure any structure three-dimensionally, regardless of the angle at which the specimen was cut.

This report describes the method for three-dimensional reconstruction and measurement, some of the new anatomic findings from three-dimensional study of temporal bones, and the implications of this new technique.

MATERIALS AND METHODS

Temporal bones with interesting anatomic and/or pathologic features are studied, and decisions are made as to the advisability of reconstructing and measuring selected structures and studying their anatomy and pathologic characteristics by means of computer-aided reconstruction and measurement. The basic equipment and methods used for these studies are as follows.

Equipment consists of a personal computer (NEC 98-XA), a high-resolution (1,120 x 750 pixels) 14-inch color

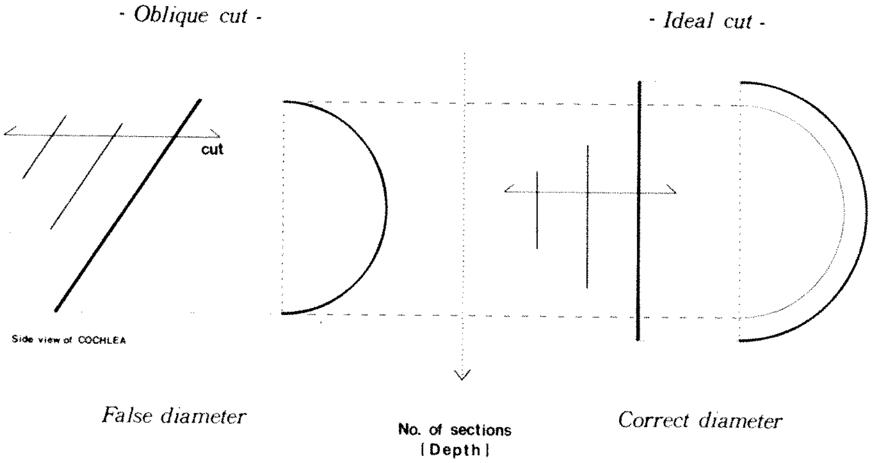

Fig 23. Schema of two-dimensional graphic reconstruction of cochlear turns. If cochlea is cut obliquely, apparent diameters of turns are smaller than actual diameters. This would account for difference in total length of cochlea measured by two-dimensional and three-dimensional graphic reconstruction methods. (From Takagi and Sando.[126])

CRT, a digitizer (Hitachi HDG-1111), an x-y plotter (Roland DXY-980), and a printer. The resolution of the digitizer is set at 0.1 mm.

One of the authors (A.T.) developed the software for three-dimensional reconstruction and measurement of temporal bone structures, using a BASIC interpreter and its compiler. This software enables us to rotate, enlarge, reduce, and move the three-dimensional figures freely. Furthermore, while viewing figures on the CRT, we can identify any point in three dimensions by moving the cursor to indicate the x and y coordinates on the digitizer tablet and then moving to the next x-y plane to obtain the z coordinate, displaying it in a different color. This means that three-dimensional morphometry can be done on the CRT screen. With this method, we can measure the following parameters in three dimensions: length, angle, surface area, and volume.

The first step in three-dimensional reconstruction of the temporal bone is to place reference marks in each histology section. Before the specimen is cut, the surface of a rounded needle (25 gauge) is coated with Magic Marker ink and then inserted into the celloidin block, guided by holes in a wooden block placed over the specimen. The insertion of the needle coated with Magic Marger ink is repeated several times for each hole to ensure good staining. These needle lines are made parallel to each other and as close to perpendicular to the cutting surface as possible at three or four points near the bone. The black Magic Marker ink remains around the edges of the hole in the celloidin, even after cutting and staining, so that the reference marks can be identified in each of the finished slides.

When the histology sections are cut, their thickness is recorded. If the thickness of the sections is changed during cutting, this also is recorded. Then, every tenth or fifth section is stained for reconstruction of large structures; every third, every other, or even every section is stained for reconstructing relatively small structures.

Computer-Aided Graphic Reconstruction. Each stained histology section to be used for reconstruction is projected onto paper by a 35-mm slide projector. The magnification is chosen according to the size of the structure to be reconstructed, and the particular structures we desire to study, as well as the reference marks, are traced onto a piece of paper. One piece of paper is used for each histology slide. Then, the papers are examined carefully, realigned, and stacked in the order in which the histologic sections were cut. This process is important, especially in sections with artifacts such as creases and distortions, because these could cause the reconstructed image to be distorted in shape if it was reconstructed only according to the original reference marks. Then a final set of reference marks is made on these papers.

Finally, we enter the data into the computer by tracing each structure on each paper on the digitizer, also entering information regarding the thickness of the section as the z coordinate; this is necessary so the dimensions of each structure can be calculated by the computer. Information regarding magnification of the slide is entered as well. The computer then generates the three-dimensional image of the structures on the CRT in the form of a wire frame model seen in perspective. Different structures can be distinguished clearly, because the outline of each structure is in a different color.

The reconstructed image can be rotated easily and can be viewed from any distance (ie, it can be viewed from any direction and at any magnification).

Although the primary coordinates of a section are defined by the angle at which the specimen was cut, we can define an arbitrary set of coordinates to view the specimen from another angle. This is useful in that it permits us to draw lines in the third dimension to the two-dimensional view.

Computer-Aided Three-Dimensional Measurements. Parameters such as length, surface area, volume, and angle can be calculated mathematically by the computer. Length is represented by the distance between two sets of x-y coordinates and can be calculated by moving from one point in an x-y plane to another to obtain the distance along the z axis. To measure a curved area, the area is divided first into many triangles, each defined by three points. The area of each triangle is calculated, and the total surface area can be obtained by summing all the areas of these small triangles. This is done automatically by the computer, once we enter the appropriate points into the computer. Volume is calculated by entering the areas in each x-y plane and then entering the distance between each x-y plane along the z axis. Angles between two lines, between a line and a plane, and between two planes also can be calculated from the coordinates of the points composing those lines or planes.

By these methods, the following measurements were performed.

1. The total length of the cochlea was obtained by mea-

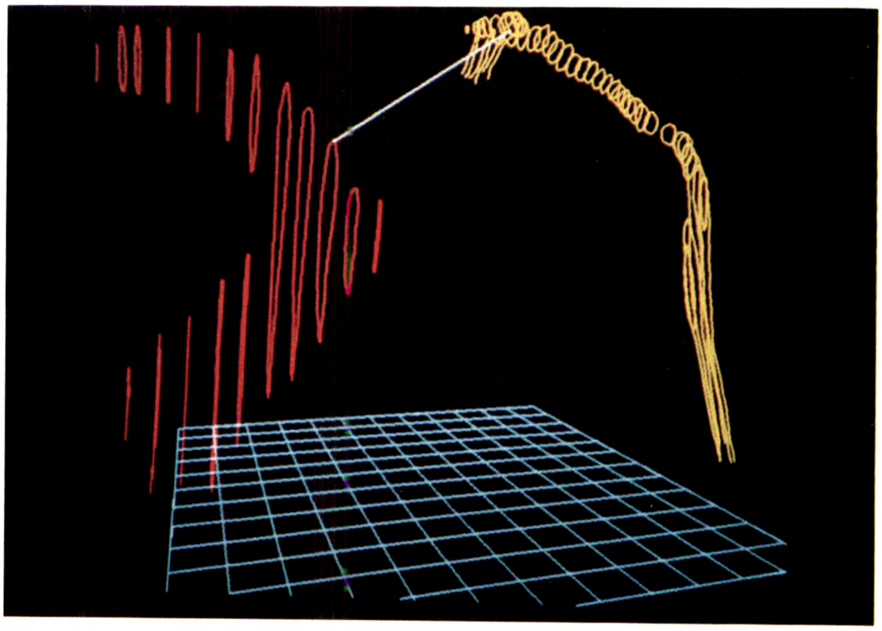

Fig 24. Three-dimensional measurement of distance (10.1 mm) between internal carotid artery (red) and geniculate ganglion of facial nerve (yellow).

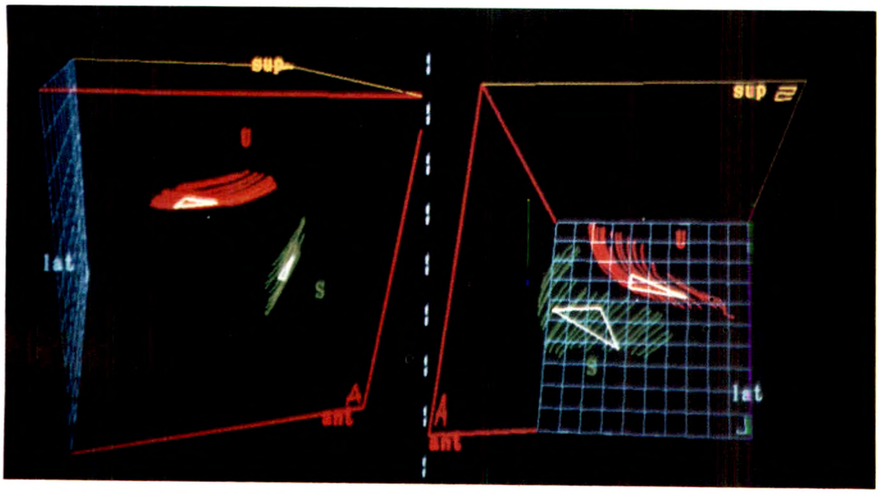

Fig 25. Spatial relation of utricular and saccular maculae, viewed anteriorly (left) and medially (right). Note that maculae do not lie at right angles to each other, but 68.2° apart in this case (left). ant — anterior; lat — lateral; sup — superior; U — utricular macula; S — saccular macula; triangles — planes of utricular and saccular macula, respectively. (Reprinted with permission from Takagi and Sando.[128])

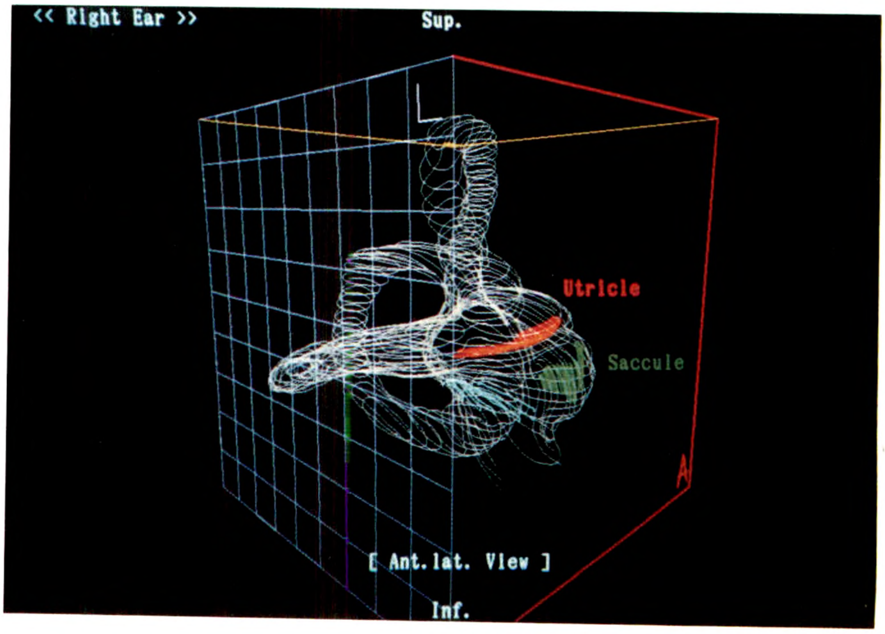

Fig 26. Anterolateral (Ant. lat.) view of semicircular canal and utricular macula of normal right ear. Note that lateral semicircular canal and utricular macula (red) are parallel to each other in one plane. Sup. — superior, Inf. — inferior, green — saccular macula.

suring the length of the cochlear spiral. It was calculated by entering the point of union of the pillar cells in each section sequentially.

2. The shortest distance between the internal carotid artery (ICA) and the facial nerve (geniculate ganglion, GG) was calculated by plotting the two nearest points on images that included the ICA and GG.
3. To obtain the angle between the utricular macula (UM) and saccular macula (SM), we first defined the plane representing each macula by entering three points on the macula into the computer. For the SM, a plane for its midportion was assumed, because it curves significantly. This measurement was made in four temporal bones.
4. The anatomic relation of the UM to the lateral semicircular canal (LSC) also was evaluated three-dimensionally.

RESULTS

1. The length of the cochlea in three dimenisions was 36.4 mm in one case. The value measured by the two-dimensional cochlear graphic reconstruction method in the same case was 30.8 mm (Fig 23[126]).
2. The shortest distance between the ICA and GG was found to be 10.1 mm, measured three-dimensionally[127] (Fig 24).
3. The angle between the UM and SM proved to be less than a right angle: 77° (average of four cases) (Fig 25[128]).
4. The planes of the UM and the LSC were found to be almost parallel[128] (Fig 26).

DISCUSSION

The total length of the cochlea was found to be 5.6 mm (15.4%) longer than the value calculated by two-dimensional reconstruction.[126] The most probable source of this serious difference lies in the assumption in the classic two-dimensional reconstruction method that the cutting angle, which is usually parallel to the middle cranial fossa, is also parallel to the long axis of the cochlear modiolus, though these two are quite different from parallel to each other. This results in reconstructing the cochlea from the specimens that are cut obliquely to the modiolar axis and have smaller diameters than the actual ones.

The value for the shortest distance between the ICA and GG obtained in this study is considered to be one of the most precise values, because the relationship between them could be assessed fully by use of various magnifications and viewing angles. Such information is useful to surgeons operating on the cranial base.

The angle between the UM and SM was found to be less than a right angle; this is a new finding,[128] as the angle was believed to be 90°.

Another surprising finding is that the planes of the LSC and UM are almost parallel in one plane.[128] This interesting and significant fact leads us to speculate that these vestibular end organs may have a function as yet undiscovered.

These new findings could have been obtained only by use of our computer-aided three-dimensional reconstruction method. A new technique for generating three-dimensional images by computed tomography has been developing recently. But the application of this method to temporal bone study is limited, because the resolution obtainable by the most advanced CT methods (0.5 mm) is still too coarse to make precise definition of inner ear structures possible. For instance, the diameter of the semicircular canals or the short diameter of the stapes footplate would have to be recognized from only two or three tomographic slices. Further, discrimination of soft tissue structures, such as the membranous labyrinth, is difficult with CT because of the small differences in radiodensity between them and the surrounding structures. Thus, histopathologic study of the temporal bone is indispensable to precise morphometry of its structures. Further, the method we describe here seems to be the best available at present.

The advantages of a three-dimensional reconstruction technique using a computer to study temporal bone histology include the following:

1. The ability to visualize the real three-dimensional shapes of structures in the temporal bone.
2. The ability to appreciate the three-dimensional relationship between structures, viewed from any direction and under any magnification by easy manipulation. Because the reconstructions are transparent, structures behind the plane being viewed can be seen. This makes it easier to visualize many relationships that cannot be seen so readily in the intact specimen.
3. The ability to measure the dimensions of structures in three dimensions, regardless of the cutting angle. This enables us to do quantitative morphometry using temporal bone serial sections.

DEVICE FOR MAKING REFERENCE MARKS

Yasuya Nomura, MD

Computer graphics have become remarkably sophisticated, and such technology can be applied as a tool in temporal bone research. Reconstruction of any part of the ear is possible, from serially sectioned specimens to three-dimensional views. Shapes and measurements obtained by computer graphics are far closer to those of real temporal bones than are those obtained using other methods, if outline curves are input accurately and the necessary reference marks are added. Reference marks must be placed on celloidin specimens in order to reconstruct graphics from information already input to a computer.

We have developed a precision drilling device to make these reference marks.[129] The principle is to drill holes in a celloidin block before sectioning. The device has three parts: a worktable, a stand or column, and a motor-driven unit. A sliding microtome is placed on the worktable (Fig 27A). The drive unit can be rotated away from the sliding

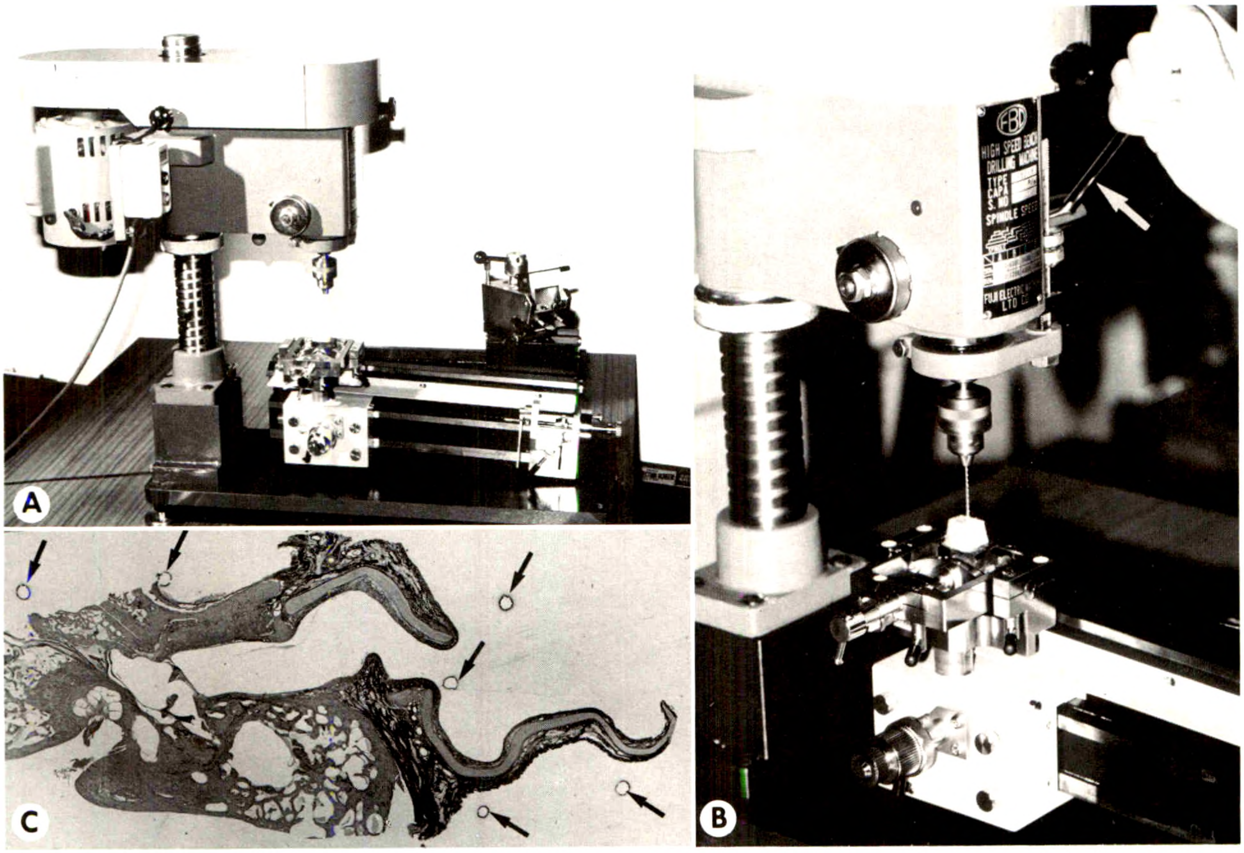

Fig 27. A) Precision drilling device for making reference marks in celloidin block. Sliding microtome is placed on worktable, and a motor-driven unit is placed above. B) Celloidin block is drilled by pulling lever (white arrow) down. C) Human temporal bone celloidin specimen. Arrows — holes made by device.

microtome when it is in use, and also can be moved by pulling a lever down. The amount of downward movement is registered on a scale attached to the machine.

The celloidin block is sectioned by the sliding microtome until the final plane for continuous sectioning of a temporal bone is determined. Then the knife is removed as a safety precaution, and the drive unit is rotated above the celloidin block. The top of the block is a horizontal plane, and a twist drill (6,000 rpm) is directed perpendicular to the plane. Several holes are made within or close to the temporal bone by pulling the lever down (Fig 27B). The diameter of the holes is 1 mm. Then the drive unit is rotated away from the block. Sectioning of the celloidin block then is continued in the same manner.

Photomicrographs are taken from hematoxylin and eosin-stained preparations and fed to an image scanner (Fig 27C). Outline curves of the desired structures are traced with a stylus pen from images that appear on the scanner screen.

The reference marks serve as keys when outline curves are being traced. Surface reconstruction is done by the method of Christiansen and Sedersberg[130] or other methods.

MICROSLICING

Gregory R. Bock, PhD, DSc

Traditional techniques of decalcifying, embedding, and sectioning the human temporal bone have greatly increased our understanding of human cochlear anatomy, but they have several disadvantages. Gross (three-dimensional) examination of the inner ear is not possible. Decalcification requires prolonged immersion in acid, which can produce artifactual tissue alterations. Dehydration and embedding take months to complete, so that data usually cannot be obtained before about 9 months after removal of the temporal bone. Finally, the destructive nature of serial sectioning precludes the subsequent application of other techniques (eg, ultrastructural observation) on the same material.

In order to overcome some of these problems, Leslie Michaels et al[131] from the Institute of Laryngology and Otology, London (England), developed an alternative technique for processing human temporal bones. The undecalcified bone is cut on a precision annular saw into microslices 1 to 3 mm thick. These slices then can be subjected to gross examination by light microscopy. Decalcifying and embedding such slices is accomplished much more rapidly than with the whole temporal bone. Following the initial sectioning, pieces of membranous labyrinth can be removed for surface observation.[97]

Bredberg et al[132] have evaluated the tissue alterations produced by application of the microslicing technique. Not surprisingly, there is evidence of mechanical distortion of the membranous labyrinth near the cut, and also of detachment of membranes from bone. Scanning electron microscopic observation of the surface of the organ of Corti shows clear contamination by bone dust near the cut. Transmission electron microscopy can show excellent preservation of cells more than 1 mm away from the cut surface, and it therefore has been suggested[133] that 5-mm microslices are preferable if transmission electron microscopy observations are to be made.

LIGHT AND ELECTRON MICROSCOPY ON THE SAME TEMPORAL BONE

HAROLD F. SCHUKNECHT, MD

A method has been developed recently at the Massachusetts Eye and Ear Infirmary for studying 20-μm celloidin-embedded tissue sections by transmission electron microscopy. The method is suitable for temporal bones removed within 4 hours of death, but preferably the inner ears would have been perfused with glutaraldehyde fixative solution or fixed in formalin soon after death. After fixation they are decalcified in EDTA, embedded in celloidin, and further prepared in the usual manner for light microscopic study. To prepare the tissue for electron microscopic study, the celloidin is removed and selected areas of the section are mounted in Epon for ultrathin sectioning.

To remove celloidin, the slides are cleaned with a potassium dichromate solution and coated with gelatin (Wyllie technique), labelled with a diamond pencil, and coated with albumin. The tissue is placed into a dish of 80% ethyl alcohol, floated onto cigarette paper, trimmed, placed on the slide, blotted with bibulous paper, and pressed with a roller to remove air bubbles. The tissue section, which is still backed by cigarette paper, is placed on a paper towel, covered with a piece of bibulous paper that has been dipped in 10% formalin, and pressed for 20 to 30 minutes under a wooden block and a lead weight. The tissue section is placed into a solution of 80% ethyl alcohol, whereupon the cigarette paper separates from the tissue and can be removed. The sections are transferred through solutions of 95%, 100%, and 100% clove oil and left in clove oil overnight. The section is then transferred through solutions of 100%, 100%, 95%, 80%, and 50% distilled water. It then can be embedded in Epon for electron microscopic study.

CENTRAL NERVOUS SYSTEM STUDIES

ILSA R. SCHWARTZ, PHD

Although this Workshop concerns temporal bones and what they can contribute to our study of auditory and vestibular function and dysfunction, temporal bones house only one portion of these systems. The ear does not operate in isolation. Signals from the auditory and vestibular apparati must be sent to the brain for interpretation. Signals from the brain to the ear modify the ear's function. Thus, any consideration of temporal bone disease is really only a fraction of the story of auditory or vestibular dysfunction. Since our primary reason for studying the temporal bones is to learn about auditory and vestibular processes, the correlation of brain and temporal bone findings is essential.

What kinds of things can we learn from correlated brain and temporal bone studies? If temporal bone findings appear normal in a patient with diagnosed hearing or vestibular dysfunction, the site of the lesion may be in the CNS. Without brain specimens the site(s) of the lesion cannot be established. If both brain and temporal bone specimens are anatomically normal, the disorder may have a metabolic basis that special staining or immunocytochemical techniques could elucidate.

The effects of many systemic diseases on the auditory and vestibular systems have not been well studied. Systematic evaluation of auditory and vestibular CNS areas and temporal bone specimens from patients with such diseases could lead to the recognition of additional causes of auditory and vestibular dysfunction that presently are classified as idiopathic.

A major contribution of temporal bone analysis is the verification of the correctness of diagnoses and treatments of conditions, often occurring at several different times during the donor's life. The evaluation of both brains and temporal bones allows the recognition of contributing factors that easily could be overlooked if only temporal bones were examined, although the examination of substantial numbers of temporal bones in the absence of brain examination or the examination of substantial numbers of brains in the absence of temporal bone studies is still highly preferable to the total absence of such correlative studies.

What kinds of questions should be asked about temporal bone and CNS specimens? Are the gross structures normal in size? Symmetric? What are the relationships to major blood vessels? Is there any feature related to pigmentation of the donor? (Skin, eye, and natural hair color should be part of the record.) Are all the auditory and vestibular cell groups present? Are they normal in appearance (ie, are the number, size, and cytoarchitectural arrangement grossly normal)? Are any changes relatable to age or any known disorder? What is the nature of any cellular changes present? What is the time interval between the first diagnosis of hearing or vestibular loss and the collection of the specimen? Could any changes represent early stages in disease processes whose end point might be auditory or vestibular dysfunction? Could any of the changes be related to surgical or medical treatments received by the patient for any condition? Is there any feature that can be correlated with some documented auditory or vestibular functional deficit?

What are some current issues that could be addressed with such specimens? Are there any systematic changes in the brains of patients treated with ototoxic drugs, or widely used drugs that have not yet been associated with ototoxicity? Which of these is secondary to cochlear loss? Are any of the changes attributable to primary central effects of the drugs?

Are there any systematic differences in specimens collected from widely different locations that could reflect environmental influences?

Are there any systematic differences in specimens that can be related to age, sex, pigmentation, or other genetic factors?

With regard to cochlear implants, there are a few implantees who show exceptional improvement, including open speech recognition. Is there anything in the temporal bones or brains of these patients to explain these outstanding results? Which, if any, features are absent in implantees who achieve only moderate improvement or none at all?

A corollary of these last questions is, what is the minimum number of cells or fibers seen in temporal bones from persons with "good" hearing?

With regard to tinnitus, a recent hypothesis[134] suggests that unusual relationships between blood vessels and the auditory and vestibular nerves may result in pulsatile vascular compression of the nerves that alters the temporal pattern of discharges and results in tinnitus. Thus, it is important to obtain specimens in which these relationships are preserved and can be assessed.

Are there any special problems related to specimens from AIDS patients or those with similar diseases? All specimens that may be contaminated with slow viruses or vectors of fatal diseases must be handled with care. Standard fixation methods may not kill these agents, but these risks have not prevented other organs from these patients from being examined to provide clues as to the sequence of events in the disease process.

Specimens from AIDS patients might represent an unusual opportunity to examine temporal bones and brains in relatively young adults whose auditory and vestibular functions have spanned a wide range and who frequently may have been evaluated relatively recently because of military service or because of general neurologic workups related to AIDS.

What portions of brain specimens should be preserved, and in what form? Nervous tissue is subject to rapid postmortem deterioration. Thus, delays between death and fixation of brain tissue will reduce the quality of the information that can be obtained from the specimen. However, even in material that has suffered substantial deterioration, certain features can be determined. These features include gross anomalies of the brain, the anatomy of major blood vessels, the presence or absence of major cell groups, and some indication of the relative numbers and types of cells present.

Brain tissue normally is obtained at autopsy and preserved by immersion fixation in formalin. Given the mass of the brain, superficial structures are fixed more rapidly, and therefore better, than deep structures. Given an interest in the deeper auditory and vestibular structures as well as in the eighth nerve as it runs from the inner ear to the cochlear nucleus, it would be important to exercise care in removal of the brain, carefully cutting the eighth nerve so that both proximal and distal stumps could be studied (the distal stump would be part of the temporal bone core), to perfuse it with fixative if possible, or to bisect the brain at the midline to enhance rapid penetration of fixative.

Ideally, the whole brain should be preserved. However, space limitations, the time and expense of processing, and the fact that some brains will have been sliced already for examination at autopsy may limit the amount of tissue that can be recovered, kept, or processed. It would be important to document the gross features of the whole brain: weight, dimensions, asymmetry, lesions, and any unusual features. Photographs of dorsal, ventral, rostral, and caudal as well as midline views could be made to substantiate any written observations and provide an opportunity for reexamining additional aspects at some future time. If whole brains cannot be sectioned, serially ordered slices through the brain, from which selected auditory and vestibular areas might be removed for further processing, are probably the best alternative. Slices through the brain stem at the level of the trapezoid body would include the cochlear nuclei, the superior olivary complex, and the vestibular nuclei. More anterior slices would include the lateral lemniscus and the inferior colliculus. Brain stem slices also would include the ocular motor nuclei. Slices through the cerebellum would include regions receiving direct labyrinthine projections as well as regions projecting to and from the vestibular nuclei. Sections through the hypothalamus would include the medial geniculate, and sections through the middle level of the thalamus would include the auditory radiations and might extend to the auditory cortical areas around the lateral temporal gyrus. Given the tonotopic nature of the auditory projections, it would be important to preserve the rostral-caudal sequence of the successive sections through each major nuclear area. Similar position-specific information also would be of value in the vestibular system. Thus, simply taking a random piece through any auditory or vestibular structure would be the least valuable form of preserving the tissue, but still better than nothing.

What kinds of studies have been performed correlating changes in temporal bones and the CNS? Most have been experimental studies in animals. There have been relatively few such studies, and almost all have looked at associations between pigment mutants or behaviorally detectable mutants and altered hearing, balance, and position functions.[135-140]

There have been even fewer studies of human material. Most have been independent examinations of the auditory or vestibular CNS[141-148] or of temporal bones.[43,149-154] In a few instances both brains and temporal bones from the same individuals have been studied,[155-159] and some studies are under way to collect brains and temporal bones in a systematic way (R. Hinojosa, personal communication, 1988).

There are a number of reasons why so few correlated studies have been performed. Although valuable information can be obtained from brains harvested a number of hours after death, investigators prefer to work with better-preserved tissues. Thus, animal studies in which brain tissue is obtained from animals killed by perfusion with an appropriately chosen fixative, or by euthanasia after live tissue has been removed and immediately frozen, provide the best choices when the questions to be asked require special preparation techniques, eg, questions about ultrastructure or immunocytochemistry. In order to preserve human brain tissue to make it suitable for electron microscopic[160] or immunocytochemical study, it must be fixed (or frozen) within a very short time after death. This requires 1) a timely identification of prospective donors so that consent forms can be obtained premortem and 2) an investigator and/or team who can be on site and prepared to act immediately once death occurs. The manpower and commitment necessary are likely to be found only in the context of a research program with a specified target group of subjects and a well-defined research question.

What kinds of studies are now possible with newer methods? What limitations apply to them? A variety of histochemical, immunocytochemical, and autoradiographic light and electron microscopic techniques have been developed in recent years that allow neurons to be defined in terms of their chemical as well as their morphologic characteristics. These techniques are based on the retention of enzymatic activity within the neuron (eg, cholinesterase activity), on the ability of the living cell to accumulate a specific substance (eg, high affinity uptake of amino acids), or on the ability of an antibody to recognize and bind to some specific compound within the cell (eg, glutamic acid decarboxylase). Histochemical reactions produce a colored or electron-dense deposit that can be detected by either light or electron microscopy. Accumulated substances may be labeled with radioisotopes so that their presence can be detected autoradiographically. Bound antibodies can be detected by second antibodies that recognize and bind to the original probe (the first antibody) and that in turn can be conjugated to an enzyme (horseradish peroxidase) or an electron-dense marker (colloidal gold) that can be detected by light or electron microscopy.

Most of these techniques have stringent requirements as to the state of the tissue to which they are applied. Clearly, methods that require living tissue will be impossible to carry out on human specimens unless they are excised during surgical procedures for conditions that may or may not affect auditory and vestibular function (eg, cancer). The only such tissues likely to be available during surgical procedures would be peripheral auditory and vestibular structures.[161] Some methods can be applied to frozen or specially fixed tissue.[162] Thus, meaningful studies of human material would require major commitments of effort to orchestrate the selection and monitoring of terminally ill patients who are potential donors and ensure the presence of investigators who can remove and process the donated tissue immediately postmortem.

Some antigenicity is known to survive standard temporal bone formalin fixation and up to 8 months of decalcification in EDTA,[163] but the survival of antigenicity in brain tissue must be determined individually for each of the antibodies to be used.

Important information about synaptic connections also can be obtained with updated classic methods. Golgi-impregnated neurons can be treated to convert the impregnation products to fine-grained metallic precipitates that can be viewed electron-microscopically to identify the ultrastructural features of the soma and processes of the impregnated neurons. This also allows the identification of cells and processes adjacent to or synapsing upon the surfaces of the impregnated cell. More simply, samples of human brain tissue have been divided, and half were treated for Golgi impregnation and the other half for ultrastructural analysis.[160] Preservation of the eighth nerve also can be improved by perfusion of the perilymphatic space with fixative within 1 hour after death.[40,65,161]

CONCLUSIONS

There is a major need to obtain brain specimens that can be correlated with medical histories of auditory and vestibular function and with the temporal bone findings in the same individuals.

Important information can be obtained from brain specimens that are not fixed until several hours postmortem and that are preserved by standard methods of immersion fixation in formalin.

New methods of neuronal analysis require extensive premortem planning to ensure rapid harvesting and appropriate preservation and/or fixation of the donor tissue.

Systematic correlative studies of peripheral and central portions of the auditory and vestibular systems in both animals and humans hold great promise for improving our understanding of normal and pathologic auditory and vestibular function.

RELATED STUDIES OF THE CENTRAL NERVOUS SYSTEM

HORST R. KONRAD, MD

Few pathologic processes involve only the sensory end organ without affecting the central portions of a sensory system. An excellent example of this is found in the visual system, in which dysfunctions in the end organ at an early age profoundly affect central visual development. In order to obtain information about the normal anatomy and function of a sensory system as well as the effect of disease processes on such a system, we must obtain samples of the central connections as well as the end organ.

If we are interested primarily in hearing and balance, then in addition to the temporal bone, we must obtain the entire brain stem and thalamus and samples of the cerebellum and the temporal cortex. Since balance also strongly involves eye movement control, we must be able to sample occipital, parietal, and frontal cortices, as well as the cerebral white matter.

Ideally, we should have the entire brain for study, since many of the central connections (especially the connections to association areas and between sensory systems) still are incompletely understood. If we cannot obtain the entire brain for study, we should at least be able to sample the brain stem, cerebellum, and temporal, parietal, and frontal cortices through an external incision for removal of the temporal bones. The brain samples can be obtained through a bone flap similar to the one used for a middle fossa craniotomy.

Before we study disease processes, it is important to study first the normal central auditory, vestibular, and eye tracking systems. This could be set up as a study similar to Dr Hinojosa's central auditory studies (NIH grant 27047, still in progress). By removing the brain stem, we can perform cell counts on the vestibular nuclei and oculomotor nuclei and evaluate the pontine reticular formation and the medial longitudinal fasciculus. The nuclei of Cajal and Darkshevich also can be evaluated. If the entire brain is available, then the cerebellar nuclei and the cerebellar cortex can be sampled and the thalamic cell stations (nucleus ventralis posterior lateralis pars oralis) studied. The superior sylvian gyrus and the inferior intraparietal sulcus can be sampled to study vestibulocortical projection areas. For the eye tracking system, the ascending visual projections, and the visual, parietal, and frontal cortices are all important. The lateral geniculate and superior colliculus are important cell stations that need to be evaluated. To do an adequate sampling of such data for statistical analysis is an enormous undertaking, particularly since age appears to affect these systems, and norms would have to be evaluated for several age groups. However, it is important to do such a survey, since interpretation of disease processes will depend on a knowledge of normal anatomy.

Cell counts in nuclei may yield much useful information; however, cell density estimates in diffuse areas such as the reticular formation and cerebral cortex have not proved useful in neuropathology in the past. Not only are density studies difficult because of variable shrinkage, but in many CNS diseases, cell density and cell numbers are not altered. The factors responsible for the disorder are caused by changes in neurochemicals or in synapses rather than in the cell body as observed by light microscopy.

Concomitant studies in animal models should be integrated with human studies to shed light on observations made in humans. Studies on development and aging are already under way in such models.

Future studies of homogeneous groups of patients thoroughly evaluated during life will add to our knowledge of human disorders of the auditory, vestibular, and eye tracking systems.

HISTOCHEMISTRY OF THE HUMAN TEMPORAL BONE

YASUYA NOMURA, MD

The main purpose of histochemistry is to localize and characterize chemical substances and enzymes within tissues. Although the inner ear is encased within the hardest bone of the human body, it can be studied histochemically. Histochemical studies of the human temporal bone have two purposes. One is to investigate the distribution and localization of certain substances or enzymes in the cells within the ear; staining of glycogen in the hair cells and the study of oxidative enzymes are in this category. The other purpose is to examine certain tissues with use of staining substances or enzymes absolutely or relatively specific to a certain tissue to clearly visualize it. For example, the course and distribution of capillaries in the membranous labyrinth are visualized easily upon staining with alkaline phosphatase.[164]

A cryostat is used routinely for sectioning tissues in histochemical studies, and the thin sections are transferred to staining solution before incubation. Bony tissues must be decalcified before sectioning in the cryostat, for which EDTA solution is commonly used because it preserves enzyme activity. There are several methods of preparing human temporal bone tissues for demonstrating enzyme activities, two of which are outlined below.

PERFUSION OF PERILYMPHATIC SPACES OF COCHLEA

Staining solutions are perfused into the cochlea through a polyethylene tube introduced into either the oval window or the round window. The other sides of the windows are removed as an outlet for the solution. The solution flows within the cochlea in response to hydrostatic pressure. After staining is completed, the temporal bone is decalcified, dehydrated, and embedded in celloidin for serial sectioning.

This technique is especially useful in demonstrating enzymatic activities in the organ of Corti, because the staining solution passes easily into the cortilymph from the scala tympani.

SURFACE SPECIMEN TECHNIQUE FOR HISTOCHEMISTRY

The inner ear is composed of several lamellar structures that can be used as sectioned slices after dissection. A fresh temporal bone is roughly dissected under a surgical otoscope to expose the membranous labyrinth with or without fixation. Then fragments of temporal bone or partially opened bones are soaked in histochemical staining solutions that must be kept cold during staining to lower enzyme activity. Although the inner ear is spacious and composed of thin membranous structures, some time is required before the staining solution penetrates evenly into the bones or bone fragments. Enzyme reactions in tissues should not occur before thorough penetration of staining solution; otherwise, only the surface of the fragments or

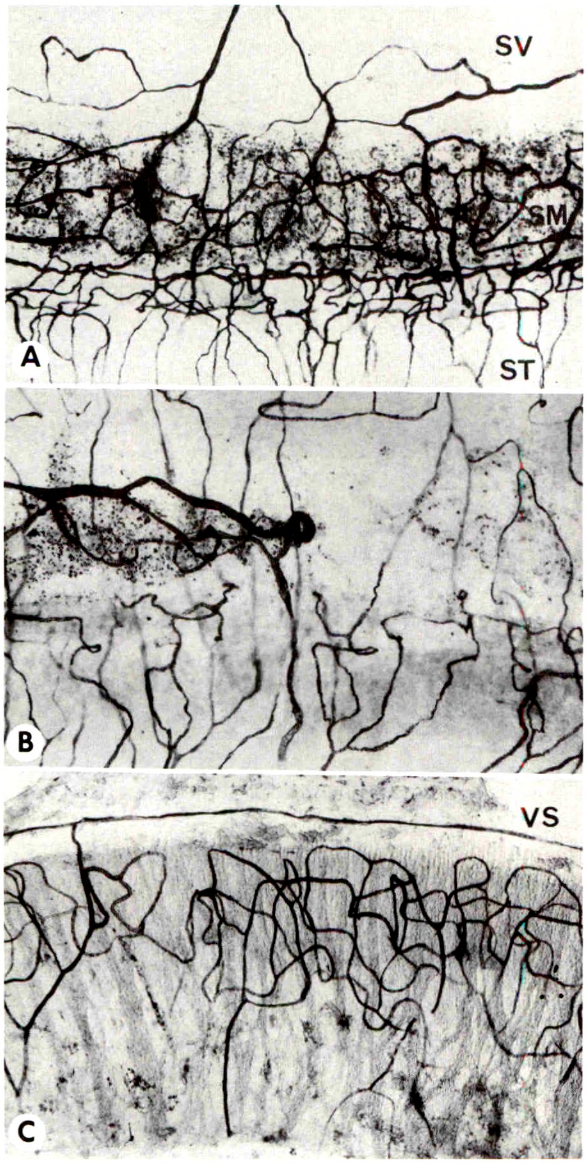

Fig 28. Capillary distribution. A) Blood vessels in stria vascularis and spiral ligament of 86-year-old man (alkaline phosphatase staining). Vessels are stained red by use of coupling azo-dye method. SV — scala vestibuli, SM — scala media, ST — scala tympani. B) Strial atrophy in 86-year-old man (alkaline phosphatase staining). Strial capillary is present in partially atrophied area of stria vascularis (left half), but missing in totally atrophic area (right half). C) Capillary networks in osseous spiral lamina–basilar membrane (basal turn) of 48-year-old woman (alkaline phosphatase staining). VS — vas spirale.

bones will be stained. This is the main reason for maintaining tissues and solutions at low temperature.

As an example, histochemical studies of capillary distribution in the human inner ear and the efferent nerve fibers are described below.

Capillary Distribution. The capillaries in human temporal bone can be demonstrated by use of histochemical techniques. It is known that the capillary wall has alkaline phosphatase activity, and therefore, after dissection of the temporal bone, the tissues are fixed with cold formalin and transferred to cold aklaline phosphatase staining solution. The azo-dye staining technique is preferred, since it requires only one solution. Incubation is carried out at 4°C. Incubation time ranges from several hours to overnight to allow the tissue to react with the substrate at such a low temperature. After staining is completed, the tissues are washed and fixed for further dissection. Thin sections are dehydrated in a graded alcohol series and mounted in resin for light microscopic observation (Fig 28). The stained tissues are embedded in Epon for electron microscopic observation.

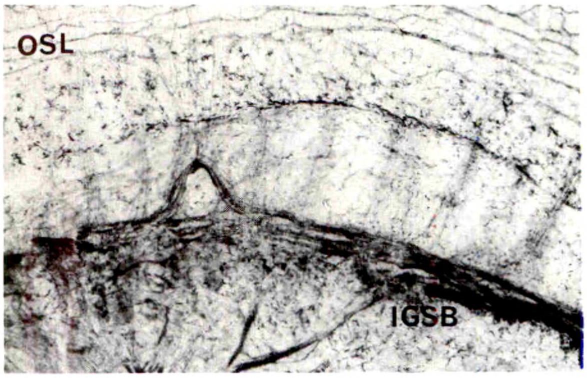

Fig 29. Efferent fibers in cochlea of 43-year-old man (acetylcholinesterase staining). Efferent fibers in osseous spiral bundle (OSL) are clearly visualized. IGSB — intraganglionic spiral bundle.

Efferent Nerve Fibers. The efferent nerve fibers in the inner ear can be examined histochemically by use of the acetylcholinesterase staining technique (Fig 29).[165,166]

The order of steps in processing tissues for histochemistry is flexible, depending on the specific purpose of the study. If enzymes to be studied are resistant to fixative, tissues are fixed before staining for better preservation; otherwise, the tissues are stained first, followed by fixation (Fig 30).

Histochemical studies can be conducted at the light microscopic as well as the electron microscopic level. Although there are limitations because of postmortem changes, the application of histochemical methods will shed further light on study of the human temporal bone.

DISCUSSION

The method of lateral approach temporal bone harvesting as described by Drs Nadol and Konrad should increase the number of temporal bones available to researchers, since this technique should be more acceptable both to families and to morticians and does not require opening the skull as by the conventional approach. It was strongly recommended that more researchers learn this technique and use it to increase the number of temporal bones

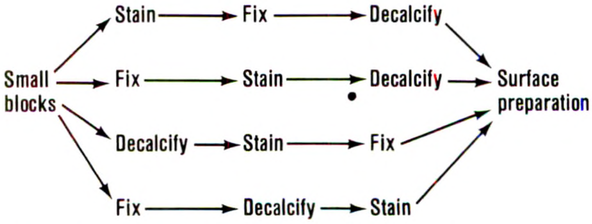

Fig 30. Order of steps in processing tissues for histochemistry.

available for research purposes. In addition, the extension of the temporal bone pathologic specimen to include portions of the CNS will enhance our understanding of the complete peripheral and central auditory and vestibular systems. The extended method of temporal bone removal together with the pharynx will enhance our knowledge of the complete tubotympanic system, including the cartilage and muscles of the eustachian tube and surrounding tissues. Microdissection, surface preparation, high-resolution scanning electron microscopy, transmission electron microscopy, computer reconstruction, and freeze-fracturing were considered to be important new methods for investigating the disorders of the human temporal bone. The methods of examination of undecalcified bones developed and used at the University of Utrecht and the microslicing techniques developed in Great Britain are available to research clinicians in the United States. The method of preparation of the human temporal bone described by Drs Schuknecht and Nadol (and similar to that described by Spoendlin), which allows investigation of the bone by light microscopy first and by electron microscopy later, should greatly improve our ability to investigate many diseases that previously could be studied only by one method in a single temporal bone. For this procedure, the bone must be fixed in glutaraldehyde and decalcified with EDTA in order to preserve the cellular detail. The current standard celloidin method of processing takes approximately 9 months, and the additional process takes only 2 to 3 months longer, using EDTA to decalcify the bone.

The Workshop conferees also agreed that studies of the CNS as described by Dr Schwartz are extremely important, since there are no normative data on the central auditory and vestibular systems correlated with peripheral sensory organs of the human temporal bone. Studies of CNS tissue would advance our knowledge about many conditions and diseases such as ototoxicity, presbycusis, genetic disorders, and AIDS, as well as the prognostic variables related to cochlear implants. It was agreed that joint studies of temporal bones and central auditory and vestibular pathways, together with the medical history and new methods of testing such as magnetic resonance imaging, computed tomography, and positron emission tomography, should be helpful in elucidating many diseases and disorders affecting the hearing and vestibular systems. The methods of histochemistry, immunocytochemistry, in situ hybridization, and immunochemistry provide the latest in technology for investigating many of these diseases and disorders.

In addition to the above methods of temporal bone pathology, the conferees added the following methods that can be used to investigate diseases and disorders of the hearing and vestibular systems: 1) autoradiography, 2) tissue and organ culture, and 3) immunochemical and biochemical assays. For example, the method of cell (or organ) culture may be helpful in determining the pathogenesis of cholesteatoma or the morphogenesis of malformations of the ear.

PREMORTEM DATA COLLECTION

HORST R. KONRAD, MD

The value of temporal bone material is related directly to the quality of information known about the patient's health and disease states. As in clinical medicine, the most important information is contained in the history, but clinical findings and results of laboratory tests are also of great value. Since the information obtained by different physicians in a patient interview varies, it is difficult to obtain complete uniform information in a large patient population. Up to now, much of the work in temporal bone pathology has been descriptive, ie, one or a few temporal bones with a specific disorder were studied and analyzed, and clinical findings were correlated with pathologic changes. We are now at a point in the development of technology at which it should be possible to obtain a large number of data about normal and pathologic processes of hearing and balance. These data should be available for statistical analysis to develop norms by age and then to differentiate homogeneous groups of patients from normal subjects.

In order to do this, we have to have a uniform minimal data set available on each patient. What that data set should include is very important, since the overall value of long-term studies is limited by the data available. If the set is very large, then the cost in money and effort in obtaining this information is large. If the set is small, vital information will not be available for some studies. The minimal set should include complete histories relating to the sensory systems and to CNS disease and injury. Family history and history of past potentially long-acting medications should be included. Physical examination of the head and neck should include an evaluation of sensory systems of taste, smell, vision, hearing, and balance and an examination of cranial nerve function, gait, posture, and cerebellar and cognitive function. In addition to tests of audiometric, vestibular, and eye movement function, fine resolution computed tomography or magnetic resonance imaging data should be available. Computer software is available for developing a branched questionnaire that can streamline data acquisition.

Since the uniform data set is so important, a consensus conference of potential participants is an important preliminary step. In large clinical studies, the participation of a knowledgeable health professional totally dedicated to collecting and maintaining an accurate data set is important. Entry of such data into a computer system, with the information computer accessible by all participants, is also important. Emerging improvements in interactive video disc technology make this an attractive method for data acquisition and storage.

DISCUSSION

The Workshop conferees agreed that careful and thorough documentation of premortem data is critical for usefulness of the acquired temporal bone. The purpose of gathering information should relate to the specific hypothesis being tested, rather than be merely to collect data in a "fishing expedition" that can be both costly and unproductive. Ideally, investigators interested in temporal bone pathology should meet to agree on a minimum data set, so that large-scale studies involving several institutions could be conducted.

TEMPORAL BONE FINDINGS OF CLINICAL RELEVANCE

HAROLD F. SCHUKNECHT, MD

Considering the effort and expense involved in the preparation and study of human temporal bones, is it a worthwhile endeavor? To be cost-effective, it must lead to improved health care. In answer to this question, let us examine the clinical relevance of some of the pathologic findings of human temporal bone studies.

MENIERE'S DISEASE

Histologic studies have shown the principal pathologic features to be endolymphatic hydrops, ruptures of the membranous labyrinth, vestibular fibrosis, distortion and atrophy of sense organs, and apical cochlear lesions. A knowledge of the pathologic changes of Meniere's disease is the basis for several different surgical procedures designed to reduce endolymphatic hydrops and thus arrest attacks of disabling vertigo.

OTOSCLEROSIS

Histologic studies have elucidated the features of oval window and round window pathologic changes, the effects of malignant otosclerosis on the inner ear, and the pathologic changes consequent to stapes surgery. These studies have demonstrated the advantages of the small-fenestra (stapedotomy) technique over total stapedectomy, the most appropriate design of prostheses based on the pathologic anatomy of otosclerosis, types of cochlear response to surgical trauma, the importance of round window otosclerosis as a cause of surgical failure, and the improbability of otosclerosis as a cause for sensorineural hearing loss in the absence of a conductive lesion and thus the irrationality of sodium fluoride therapy in such cases.

PRESBYCUSIS

Four distinct histopathologic types have been shown to occur alone or in combination. They are sensory, neural, strial, and inner ear conductive. Thus, the deafness of aging is not caused by a uniform type of degeneration with the only variable being the magnitude of change. These patterns of pathologic alterations explain the wide differences in speech-hearing of aging ears and the limitations of sound amplification.

IDIOPATHIC SUDDEN DEAFNESS

The pathologic changes in the cochlear end organ and nerve are consistent with a viral cause. Therefore, it is irrational to treat this disorder on the basis of a vascular cause or to explore the middle ear surgically in search of a perilymph fistula.

POSITIONAL VERTIGO

Histologic studies have shown that positional vertigo is caused by basophilic deposits on the cupula of the posterior semicircular canal. This knowledge has led to a surgical procedure in which the posterior ampullary nerve is sectioned to relieve this type of dizziness.

VESTIBULAR NEURITIS

Temporal bone studies have confirmed that the sudden onset of severe idiopathic vertigo of prolonged duration, in the absence of auditory symptoms, may be caused by acute atrophy of one or more branches of the vestibular nerve with or without involvement of the associated sense organs. Because the vascular anatomy is normal, the disorder is presumed to be of viral cause. Hence, after imaging methods have ruled out vascular or neoplastic disease of the posterior fossa, there can be a high level of clinical confidence in the diagnosis of vestibular neurolabyrinthitis, a usually benign disorder with a good prognosis for recovery.

BELL'S PALSY

The pathologic finding in a recent case of Bell's palsy, that is, a small round cell inflammatory reaction in the perineural sheaths of the facial nerve, supports the idea of a viral cranial nerve neuropathy as the cause for this disorder. On this basis, therapeutic regimens based on a vascular disorder are irrational, and the value of surgical decompression is questionable.

PNEUMATIZATION AND CHRONIC OTITIS MEDIA

Histologic studies have defined the areas and tracts of pneumatization and their anatomic variations that determine in large part the pathologic features of progressive bacterial infections and cholesteatomata. Knowledge thus gained provides the basis for surgical approaches effective in preventing and controlling chronic bacterial infections and cholesteatomata and their complications.

GLOMUS JUGULARE TUMORS

Glomus bodies (nonchromaffin paragangliomata) are a normal occurrence along the course of the tympanic branch of the glossopharyngeal nerve. A knowledge of the origin and growth characteristics of these tumors forms the basis for their successful surgical management.

DYSMORPHOGENESIS

The histopathologic characteristics of middle ear anomalies, Mondini dysplasia, and numerous congenital dysmorphic syndromes have been described. This knowledge provides the basis for understanding the causes for auditory and vestibular dysfunction and for predicting the feasibility of surgical rehabilitation. Furthermore, it has been shown that spontaneous CSF otorrhea and meningitis, which may complicate Mondini dysplasia, are the result of anatomic defects in the modiolus and oval window that require surgical correction.

TEMPORAL BONE FRACTURE

Temporal bone studies have demonstrated the pathologic features of transverse and longitudinal fractures of the temporal bone, the routes of posttraumatic CSF otorrhea, and the location and pathologic changes of facial nerve injuries. Transverse fractures of the temporal bone may leave weakly healed fissures, particularly in the oval window area, that may lead to recurring or persistent CSF otorrhea and meningitis and therefore may require surgical closure. The most vulnerable site for facial nerve injuries in association with temporal bone fractures is its labyrinthine segment, and when surgical exploration is undertaken it should include this region of the nerve.

ACUTE OTITIS MEDIA AND MENINGITIS

It has been shown that meningitis occurring as a childhood complication of an acute upper respiratory tract infection and otitis media is not caused by direct spread via the labyrinth, middle ear, or mastoid and therefore is probably a blood-borne infection. It is doubtful that surgical procedures, such as myringotomy or mastoidectomy, would be of any therapeutic value in these cases.

PAGET'S DISEASE

Histologic studies have failed to identify the cause for the conductive hearing loss that commonly occurs with Paget's disease of the temporal bone. Hence, surgical exploration based on the assumption that the conductive element of the hearing loss is caused by ossicular fixation and is therefore correctable is not warranted.

TUMORS OF CEREBELLOPONTINE ANGLE

The pathologic mechanisms by which these tumors cause auditory and vestibular dysfunction have been described. These tumors cause inner ear dysfunction by pressure atrophy of the eighth nerve, interference with vascular supply resulting in ischemic necrosis of the sense organs, and alteration of protein chemistry of the inner ear fluids. That these disorders may occur singly or in combination explains the various audiometric and vestibular manifestations of these tumors.

ANATOMIC VARIANTS

Temporal bone studies have demonstrated variations in the route of the facial nerve, the configuration of the ossicles, the location and size of arteries and veins, and the patterns of pneumatization. Therefore, to avoid injury to functional anatomy of the temporal bone, the otologic surgeon must be thoroughly cognizant of its variant anatomy.

COCHLEAR NEURONAL POPULATIONS

Cochlear studies have shown 1) the numbers of neurons in hearing ears as a function of age and the effect of neuronal loss on speech-hearing and 2) the neuronal populations remaining in profoundly deaf ears of different disorders. These studies provide information on how many neurons are required for effective speech discrimination and therefore provide some basis for the selection of candidates for cochlear implantation.

ACUTE SEVERE VERTIGO

Two causes for acute, severe, prolonged, single-attack vertigo have been identified; one is acute vestibular neuritis as evidenced by degeneration of a single division of the vestibular nerve, and the other is vestibular atelectasis as evidenced by collapse of the walls of the vestibular labyrinth. The absence of a vascular lesion in these causes indicates the irrationality of treatment based on vascular disease.

CURRENT STATUS OF TRAINING OF TEMPORAL BONE PATHOLOGISTS AND TECHNICIANS

JOSEPH B. NADOL, JR, MD

INTRODUCTION

In order to assess the current status of training of temporal bone pathologists and technicians, a questionnaire was sent to 14 laboratories in the United States that are actively involved in otopathology. There were ten respondents (Table 6). The responses are tabulated in Table 7. To maintain anonymity, the order of respondents is not the same as presented in Table 6.

FINDINGS

The ten respondent laboratories have been in existence for a mean of 27 years (range, 16 to 58 years). A total of 10,458 individual temporal bones have been processed by these ten laboratories. The average number of temporal bones that have been processed per year over the life of the individual laboratory ranges from five to 76 bones per year, with a mean of 38. Over the last 5 years of existence, the average number of individual temporal bones processed per year is 35, suggesting that there has been no significant recent increase or decrease in the number of temporal bones processed yearly.

The average laboratory profile among the respondents included 1.9 MD or PhD researchers, 1.7 histopathology technicians, 1.3 research fellows, 1 resident, and 0.6 medical students actively engaged at the present time in temporal bone histopathology. Over the last 10 years, there were 147 fellows who spent at least 6 months actively engaged in temporal bone histopathology in the ten laboratories, for an average of 1.5 fellows per laboratory per year. From nine respondent laboratories, of 77 fellows who spent at least 6 months actively engaged in training in

TABLE 6. RESPONDENTS
Baylor College of Medicine, Houston
University of California, Los Angeles
University of Chicago
Eye and Ear Hospital of Pittsburgh
Massachusetts Eye and Ear Infirmary, Boston
University of Michigan, Ann Arbor
University of Pennsylvania, Philadelphia
State University of New York, New York City
House Ear Institute, Los Angeles
The University of Iowa, Iowa City

TABLE 7. QUESTIONNAIRE AND RESPONSES

	Respondent											
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Mean*	*Range*
How long has laboratory been in existence (No. yr)?	16	16	20	22	22	25	27	28	38	58	27	16-58
Approximately how many human temporal bone (sets) have been processed over lifetime of lab?	80 (40)	1,215 (732)	300 (150)	1,077 (540)	1,300 (650)	300 (150)	1,400 (700)	1,040 (520)	646 (323)	3,100 (1,550)	Total = 10,458	
Average No. of bones/yr?	5	76	15	49	59	12	52	37	17	53	38	5-76
How many bones (sets) processed annually in last 5 years?	4 (2)	33	20 (10)	64	50 (25)	2 (1)	54 (27)	40 (20)	14 (7)	66	35	2-66
At this time, how many in lab?												
MD and PhD	1	1	1	1	3	3	2	2	4	1	1.9	1-4
Histopathology technicians	1	2	1	1.5	1	2	3	2	1	2	1.7	1-3
Research fellows	0	2	0	2	0	0	2	5	1	1	1.3	0-5
Residents (otolaryngology)	0	2	1	0	1	1	1	0	3	1	1.0	0-3
Medical students	0	0	0	1	0	0	0	5	0	0	0.6	0-5
Research fellows in lab for at least 6 months over last 10 yr?	2	13	1	11	2	15	28	70	3	2	14.7	1-70
Average No./yr?	0.2	1.3	0.1	1.1	0.2	1.5	2.8	7	0.3	0.2	1.5	0.2-7
How many fellows (cumulative, last 10 yr) are now actively involved in temporal bone histopathology?	1	12	0	7	2	6	4	NA	1	1		
Percent yield (fellows trained, now active researchers with 10 yr of experience)?	50	92	0	64	100	40	14	NA	33	50	44% (weighted)	
Formal training program for histopathology technicians?	N	N	N	N	N	N	N	N	N	N		

NA — not answered.

temporal bone histopathology, 34 are now actively engaged in temporal bone research (44%).

No laboratory offers a formal training program for histopathology technicians. Most laboratories obtain such technicians by recruiting individuals who are trained in histopathology and providing on-the-job training for the special requirements of otopathology.

CONCLUSIONS

From such an informal survey, only tentative conclusions can be drawn. However, it is clear that the average laboratory actively engaged in temporal bone histopathology is a relatively small operation with fewer than two investigators, one or two fellows and residents, and fewer than two technicians involved in histopathology.

The yield of future investigators in temporal bone histopathology has been relatively low, that is, approximately 34 individuals from nine laboratories over the last decade. Data were not obtained as to the present country of residence of these investigators or the percent of their professional activities devoted to temporal bone histopathology. However, if our experience pertains, the number of investigators who remain active in histopathology of the temporal bone in the United States is low indeed, and the number of such individuals fully engaged in temporal bone histopathology is even lower. It seems clear from these statistics that if we are to increase the yield of information from pathologic specimens of the human temporal bone, more attention must be paid to the training of researchers and technicians in the special requirements and procedures of temporal bone histopathology.

DISCUSSION

Following Dr Nadol's report, the Workshop conferees came to the following conclusions.

1. Many otolaryngology–head and neck surgery department chairpersons in the United States appear to lack interest in human temporal bone laboratory activity.

2. Pathologists and neuropathologists interested in temporal bone pathology and the central auditory and vestibular pathways are not being recruited to departments of otolaryngology and pathology.

3. There appears to be a lack of young, well-trained academicians to head up the temporal bone laboratories that exist today in the United States. This lack of interest is most likely related to the tendency to recruit clinically oriented otolaryngologists into academic departments today. In Japan and Europe a research background as well as clinical experience is required for an academic appointment.

4. There is at present in the United States a critical shortage of young, committed otologists and scientists dedicated to and interested in human temporal bone research. This is the perception of many of the Workshop conferees.

5. Training in temporal bone pathology today appears to be attracting foreign nationals into US fellowship programs in temporal bone pathology laboratories, who then return to their own countries to become temporal bone pathologists.

6. Many otologists in the United States have insufficient training with regard to basic knowledge of human temporal bone pathology.

FUTURE GOALS

TECHNIQUES

It was agreed that investigators in the United States have been leaders and a driving force for human temporal bone research and are well informed of the newer techniques such as the surface preparations and transmission electron microscopy. Many techniques have been developed in this country that are widely used. These techniques include reconstruction of the serially sectioned cochlea (Stacy Guild and Harold Schuknecht) and scanning electron microscopic techniques. However, there is an insufficient number of investigators using these new techniques, such as sectioning of the undecalcified bone, immunocytochemistry, and electron microscopy, to answer the important questions that remain concerning the disorders of the hearing and vestibular systems.

NATIONAL AND INTERNATIONAL COORDINATION OF COLLECTIONS AND STUDIES

The Workshop conferees recommended that a central repository be established, preferably at the Armed Forces Institute of Pathology or in one of our universities, and that a national registry be established to catalog the collections that are active as well as those that are currently inactive. A task force should be organized to investigate the possibility of a central repository and a method to coordinate these efforts in the United States, Europe, and Japan by cataloging and maintaining a simple registry of temporal bones available to researchers. The European Concerted Action Project could then be linked to a US coordinating center. There is a need for a meeting of the various institutions for coordination of this activity; this could be sponsored by either the Deafness Research Foundation or the Academy of Otolaryngology-Head and Neck Surgery. After extensive discussion by the conferees, it was concluded that the National Temporal Bone Bank Center in the United States should not be abandoned. Approximately 6,500 donors already have pledged their temporal bones to the program. It was suggested that the current four regional centers be reevaluated at regular intervals by an independent review board. The centers should be responsible for maintaining files not only of a patient's documents, but also of bones, in order to coordinate their procurement and distribution to appropriate and competent laboratories and investigators. It also was recommended that center status should not be exclusive, but be available to all qualified active temporal bone laboratories. Other interested basic science researchers, such as those in the field of temporal bone pathology, would benefit from an expanded program. The conferees agreed that there is still a great need to collect well-documented bones together with relevant brain tissue, especially from subjects who have been tested with the newer and more powerful methods now applied to both auditory and vestibular function. They strongly urge that the donor program proceed without interruption.

TRAINING

The Workshop conferees recommended the following methods to recruit and train new temporal bone investigators:

1. A fellowship in temporal bone pathology sponsored by the Deafness Research Foundation.
2. A fellowship sponsored by the American Otological Society, Inc.
3. A fellowship sponsored by the Academy of Otolaryngology-Head and Neck Surgery.
4. Possible fellowships sponsored by the Lions Club International.
5. Sponsorship by the National Institutes of Health through the following mechanisms: Clinical Investigator Development Awards (CIDAs); the FIRST Award (R29); Institutional Training Grant Awards (T32); and inclusion in unsolicited grant proposals of research positions available to young investigators who can be involved in human temporal bone research (R01, P01).

The conferees strongly recommended not only that otolaryngologists be recruited, but that pathologists, neuropathologists, and scientists who are not physicians be recruited to the field of temporal bone pathology. It also was recommended by the conferees that all residents receive some formal training in human temporal bone pathology, and that all fellowships in otology and neurotology include, as part of the curriculum, formal education and training in human temporal bone pathology.

METHODS TO STIMULATE INTEREST IN TEMPORAL BONE PATHOLOGY

The Workshop conferees agreed that the most effective methods to stimulate the young investigators are the following.

1. The active temporal bone pathology investigator should serve as a role model for the student (eg, resident, fellow, clinician, scientist). This apprenticeship method

has continued in the tradition of temporal bone histopathology research to succeeding generations of investigators since the 19th century.

2. Every resident should have some formal experience in human temporal bone pathology. This type of education should be mandatory for clinicians who are responsible for the diagnosis, management, and prevention of diseases and disorders of the hearing and vestibular systems.

3. Questions pertaining to human temporal bone pathology should be included on the otolaryngology–head and neck surgery in-service examinations and board examinations.

4. Awareness should be increased among aspiring young academicians that currently there are inadequate numbers of research projects and of researchers in human temporal bone pathology. This is an excellent opportunity for scientific contributions by young academicians.

5. A regular national and international meeting on otopathology should be held.

6. The Academy of Otolaryngology–Head and Neck Surgery should have a course at the fall meeting for continuing education on human temporal bone histopathology.

7. Short courses should be given at centers currently active in temporal bone research for those who want to learn more about histopathology or to keep abreast of the state of knowledge.

POTENTIAL AREAS FOR FUTURE RESEARCH

Since there have been no published normative data of age/sex-matched controls of human temporal bones correlated with physiologic data from the new auditory and vestibular function tests now available, this avenue of research should be a priority among investigators today.

There should be systematic comparisons of the accuracy of clinical diagnoses of otopathology in human temporal bones with physiologic, audiologic, and vestibular studies in single-blinded protocols, which now can be done with the accumulated specimens. This is important, since there are unresolved issues related to the causes of many diseases of the auditory and vestibular systems, including sudden deafness, Meniere's disease, chronic suppurative otitis media, presbycusis, progressive/fluctuating hearing loss, otosclerosis, inner ear autoimmune disease, vestibular dysfunction such as vestibular neuronitis, tinnitus, ototoxicity, and facial paralysis.

Studies of well-documented specimens from well-tested patients who were deaf could help in determining the best candidates for cochlear implants. Also, collection and study of specimens from patients who had received cochlear implants should receive high priority, in order to evaluate factors underlying the efficacy and long-term safety of the implants. Studies of human temporal bones can answer questions as to the most appropriate candidates for cochlear implants and the effect of cochlear implants on the inner ear, temporal bone, and CNS.

The effect of surgery of the middle and inner ear can be assessed only by human temporal bone research. Pathologic findings must be correlated with the results of surgery to answer the question of the safety and efficacy of these surgical procedures. Removing extended temporal bone specimens, which include skull base structures, can answer many questions related to the safety of skull base surgery.

The Workshop conferees commented that specimens from AIDS patients represent a unique opportunity to study the effects of this virus on the development and deterioration of the human temporal bone and on the auditory and vestibular systems in infants and adults.

The following are specific research questions that can be answered by use of the newest techniques.

1. The central auditory pathways can be studied along with the end organ (temporal bone) to correlate developmental anatomy and pathologic findings in auditory, vestibular, and visual centers in the brain and brain stem with the temporal bone and antemortem data. This research is extremely important for normative data, developmental anatomy, and a better understanding of the aging process.

2. The relationship of the CNS to the temporal bone end organ can be studied. Pathologic changes of the temporal bone end organ can be studied to evaluate ototoxicity, cochlear implants, AIDS, etc.

3. Innovative new imaging techniques such as confocal microscopy combined with computerized image storage capabilities (eg, laser sharp) can be used to evaluate the neural network of the immunostained brain slice for neurotransmitters and that of surface-prepared and immunostained temporal bones as described by Dr Lim.

4. Transmission electron microscopy combined with immunocytochemistry can be used in studies of disease processes such as otosclerosis in which only human temporal bones can be employed.

5. Three-dimensional reconstruction is valuable in making quantitative comparisons, especially for volume measurements.

6. Freeze-fracturing and deep etching technique can be used to determine the molecular organization of the cells and tissue in the ear.

7. High resolution scanning electron microscopy can be used to study the tip linkage system of the stereocilia, cell membrane specialization, specialized cell organelles, nerve endings, and neurotransmitter vesicles, in combination with immunocytochemistry to study neurotransmitters.

8. Sections of undecalcified bones as described by Dr Veldman of the University of Utrecht can be helpful in analyzing the mineralization of temporal bone diseases such as otosclerosis. This method can be helpful in elemental analysis of bony tissue and possibly in immunohistochemistry.

9. Combination of light and electron microscopy methods as described by Drs Schuknecht and Nadol can be used to answer questions related to many disorders of the middle and inner ear.

10. Histochemistry, immunocytochemistry, in situ hybridization, and immunochemistry of temporal bones can be used to answer many questions related to diseases and disorders of the hearing and vestibular systems, such as the pathogenesis of otosclerosis, viral diseases, autoimmunity, and cholesteatoma, or answering why certain bacteria cause otitis media when others do not by defining adhesion receptors. Many new research questions now can be asked with use of human temporal bones to investigate the etiology and pathogenesis of diseases and disorders of the ear by these techniques. Some techniques can be applied to material from past collections by use of the in situ hybridization probe.

11. Tissue or cell culture techniques can be used to study a) the behavior of the cells under defined conditions, b) interaction with implantable material for determining biocompatibility, or c) cell behavior such as in cholesteatoma.

12. Appropriate biochemical and immunochemical methods can be used to study the perilymph and to determine its composition, specific antibodies, or antigens in fresh specimens of human temporal bones.

CONCLUSIONS

The Workshop conferees agreed that there is an important need for continued studies of human temporal bones that may not be met by the few researchers currently active in this area. The conferees found that there is an apparent lack of interest among many young academicians and chairpersons of departments of otolaryngology–head and neck surgery in the pursuit of research using human temporal bones. In addition, there is a decreasing number of physicians/scientists interested in human temporal bone pathology research; this includes otolaryngologists as well as pathologists and neuropathologists. However, the Workshop conferees agreed that current research efforts in this country still maintain high standards in general and contribute in training many researchers from overseas. Although newer methods are not well utilized, the few active researchers in the United States are considered equal to others and are not behind those in other countries, such as in Europe or Japan. In addition, the conferees believed that there is still a need for certain kinds of descriptive research, but that more research focusing on testing specific hypotheses should be conducted in the future. They concluded that there is a lack of temporal bone pathologists and otolaryngologists trained in both classic and newer methods of temporal bone pathology to conduct future research in the field. In order to meet the needs of future research, the Workshop conferees recommended a number of methods to stimulate interest in human temporal bone pathology, avenues of training that can be made available to young physicians/scientists in both otolaryngology and pathology, and a list of high-priority research questions that potentially can be answered both by current collections and by temporal bone specimens that can be procured in the future.

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